
THE UNIVERSITY
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# Investigating the risk of intracranial haemorrhage or focal neurological deficit in adults diagnosed with cerebral cavernous malformation

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*To Tim, Graeme, Colin and Elspie,*

*for their love, support and encouragement*

# Declaration

I declare that this thesis is my own composition, and that none of the work herein has been submitted in support of an application for any other degree or professional qualification. The idea of investigating the risk of intracranial haemorrhage or focal neurological deficit and performing an individual patient data meta-analysis (IPDMA) was conceived by Professor Rustam Al-Shahi Salman (RA-SS), and that of comparing outcome after treatment by RA-SS and Dr Fiona Moultrie. The Scottish Intracranial Vascular Malformation Study (SIVMS) was designed and set up by RA-SS, and the SIVMS database was created by David Perry and further developed by Aidan Hutchison. RA-SS designed the literature search strategy for the systematic review, and I adapted it for the literature review chapter. I assisted RA-SS and Susanne Maxwell in collecting data for the later cohort of SIVMS adults who had been diagnosed with cerebral cavernous malformation. Professor Gordon Murray (GDM) and I wrote the protocol for the IPDMA, and I drafted the two statistical analysis plans (for the treatment-comparison and IPDMA). I extracted, checked, cleaned, analysed and interpreted the data for the two Scottish cohorts. Under guidance from RA-SS and GDM, I acted as the IPDMA co-ordinator: I invited fifteen research groups to participate in the IPDMA, designed data questionnaires for those groups that agreed to collaborate, and liaised with them throughout the duration of the project. I checked and cleaned all the data, pooled the data from the five cohorts into a single dataset, and analysed and interpreted the pooled data, according to the above-mentioned protocol and statistical analysis plan, both of which had been approved by all the contributors.

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# Abstract


## Background

A cerebral cavernous malformation (CCM) is a small cluster of thin-walled, dilated blood vessels within the brain which is prone to bleed. Although the quantity of blood leaking tends to be small, even a small intracranial haemorrhage (ICH) can result in a clinically significant neurological deficit. Because some focal neurological deficits (FND) may in fact be haemorrhages that were undetected by imaging, FND were also included in the analysis wherever possible. In Scotland, between 2006 and 2010, the annual CCM detection rate was 0.8 per 100,000 people. Since estimates of prognosis inform decisions about whether to treat CCM, it is crucial that the untreated clinical course of the disease is fully understood.

## Aim

The aims of this thesis are (i) to quantify the risk of ICH (or ICH or FND, referred to as 'clinical event') for an untreated adult within five years of CCM diagnosis, (ii) to identify prognostic factors for ICH (clinical event), and (iii) to create a model to predict, at the time of diagnosis, an individual's risk of a subsequent ICH (clinical event).

## Methods

Initially, a literature review was undertaken. Then data from adults diagnosed with CCM in the Scottish Intracranial Vascular Malformation Study (SIVMS) were analysed. SIVMS is a prospective, population-based cohort study: it includes all adults resident in Scotland at the time of diagnosis of a first-ever intracranial vascular malformation during the two five-year periods 1999–2003 and 2006–2010. Time-to-event methods were employed to compare the estimated risk of ICH (clinical event) for those who experienced a first ICH (clinical event) during untreated five-year follow-up with those who experienced a second ICH (clinical event). A statistical

challenge when analysing clinical outcomes from patients with CCM is that the outcome event of ICH or FND is comparatively rare; therefore a larger cohort of CCM patients was required to identify more robustly potential predictors of ICH (clinical event) and to create a prognostic model to predict, at the time of diagnosis, an individual's risk of a subsequent ICH (clinical event). Three research groups agreed to contribute their data to enable an individual patient data meta-analysis (IPDMA) to be undertaken.

## Results

In the two SIVMS cohorts, 136 (1999–2003) and 165 adults (2006–2010) were diagnosed with CCM. In the earlier cohort, the estimated risk of a first ICH within five years of presentation (2.4%, 95% CI 0.0% to 5.7%) was significantly lower ($p < 0.0001$) than the risk of a recurrent ICH (31.9%, 95% CI 4.5% to 59.3%), but the annual risk of a recurrence declined over the five-year period. In the same cohort, women had an increased risk of a second clinical event (log-rank $\chi^2(1) = 6.2$, $p = 0.01$). The IPDMA was based on 988 adults, 62 of whom suffered a first ICH within five years of CCM diagnosis. When the data were pooled, the estimated adjusted hazard ratio for first ICH for clinical presentation (ICH/FND vs other presentation) was 4.5 (95% CI 1.5 to 13.4) and for brainstem location (brainstem vs other location) the adjusted hazard ratio was 3.3 (95% CI 1.5 to 7.2); age, sex and CCM multiplicity did not add any additional prognostic information.

## Conclusion

In this thesis two risk factors have been identified that are independently associated with increased likelihood of experiencing an ICH (or clinical event) within five years of diagnosis. A prognostic model has been built and evaluated, based on these factors. Other areas to be explored in the future include external validation of the model and investigating the effects of (i) antithrombotic therapy and (ii) pregnancy on the progression of the disease.

# Publications and awards relating to the work of this thesis

## Papers in peer-reviewed journals

Al-Shahi Salman, R., Hall, J.M., Horne, M.A., Moultrie, F., Josephson, C.B., Bhattacharya, J.J., Counsell, C.E., Murray, G.D., Papanastassiou, V., Ritchie, V., Roberts, R.C., Sellar, R.J. and Warlow, C.P. 2012 . Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study. *Lancet Neurology*, 11, 217–224.

Moultrie, F., Horne, M.A., Josephson, C.B., Hall, J.M., Counsell, C.E., Bhattacharya, J.J., Papanastassiou, V., Sellar, R.J., Warlow, C.P., Murray, G.D. and Al-Shahi Salman, R. 2014. Outcome after surgical or conservative management of cerebral cavernous malformations. *Neurology*, 83, 1–8.

## Oral presentation at conference

Horne, M.A., Moultrie, F., Josephson, C.B., Hall, J.M., Counsell, C.E., Bhattacharya, J.J., Papanastassiou, V., Sellar, R.J., Warlow, C.P., Murray, G.D. and Al-Shahi Salman, R. 2014. Outcome after surgical or conservative management of cerebral cavernous malformations: a prospective, population-based cohort study. Angioma Alliance Scientific Workshop, 15–16 November 2012, Bethesda, MD (recipient of an Angioma Alliance trainee travel award).

## Poster presentations at conference

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Many other people have gone out of their way to help my research run smoothly. In the early days, both Aidan Hutchison and Rosemary Anderson in the Division for Clinical Sciences cheerfully and quickly answered any queries I had relating to the SIVMS database and how the study worked. Dr Susanne Maxwell and Christos Tolias collected data for both Scottish cohorts in 2013, to enable me to include the second Scottish cohort in the individual patient data meta-analysis: I am very grateful to you

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# Abbreviations

| | |
|---|---|
| 95% CI | 95% confidence interval |
| AOVM | Angiographically occult vascular malformation |
| CCM | Cerebral cavernous malformation |
| CSF | Cerebrospinal fluid |
| CT | Computed tomography |
| DVA | Developmental venous anomaly (also known as venous malformation) |
| FND | Focal neurological deficit |
| FND-NOS | Focal neurological deficit not otherwise specified |
| GP | General practitioner |
| GRO | General Register Office for Scotland |
| HADS | Hospital Anxiety and Depression Scale |
| ICD | International Classification of Diseases |
| ICH | Intracranial haemorrhage |
| IPDMA | Individual patient data meta-analysis |
| IQR | Interquartile range |

| | |
|---|---|
| ISD | Information Services Division |
| IVM | Intracranial vascular malformation |
| MRI | Magnetic resonance imaging |
| mRS | Modified Rankin Scale |
| NH-FND | Non-haemorrhagic focal neurological deficit |
| OHS | Oxford Handicap Scale |
| RCT | Randomized controlled trial |
| SAIVM | Scottish Audit of Intracranial Vascular Malformations |
| SIVMS | Scottish Intracranial Vascular Malformation Study |
| TWH | Toronto Western Hospital, Toronto, Canada |
| VM | Venous malformation (also known as developmental venous anomaly) |

# Chapter 1: Introduction and outline of thesis

Cerebral cavernous malformations (CCM) are the second most common form of intracranial vascular malformation, and their diagnosis has increased exponentially in the past twenty years, due to the widespread usage of magnetic resonance imaging (MRI). Before the availability of MRI, cavernous malformations could only be diagnosed conclusively after surgery or at autopsy; since brain imaging has become standard practice, however, many more asymptomatic cavernous malformations have been diagnosed. From the early 1990s onwards there have been a number of research papers published, but many of these have concentrated on interventional treatment or have produced conflicting evidence; consequently the untreated clinical course of the condition and the long-term patient outcome are not fully understood at present.

Intracranial haemorrhage (ICH) is one of the more potentially disabling outcomes for people who have been diagnosed with cerebral cavernous malformation. Not all haemorrhages that occur can be detected, however, since ICH identification is reliant upon timely neuro-imaging of an appropriate modality being undertaken. Therefore, whenever possible in this thesis, a composite outcome of ICH or focal neurological deficit (FND) was analysed, since the effects of FND can be of equal severity for patients, and in certain instances an FND may in fact be an unidentified ICH, if neuro-imaging either has not been performed or has been unable to detect the ICH (for example, because it has been obscured by the CCM).

The aims of this thesis are to investigate the risk of ICH or FND in adults who have received a first-ever CCM diagnosis, to identify any baseline characteristics that might be associated with that risk, and to build a prognostic model that can be used at the time of CCM diagnosis, to predict the risk of an ICH (or either ICH or FND) within

five years of diagnosis. The rationale for restricting the length of follow-up to five years is discussed at several points throughout the thesis (e.g., subsections 4.2.4, 6.6.2 and 9.2.1 below).The following questions are explored in detail:

1. What are the estimated five-year risks of first and recurrent ICH, definitely due to CCM:
    a. in two cohorts of adults newly diagnosed with CCM, drawn from the Scottish population?
    b. in five cohorts of newly diagnosed adults, from western Europe and North America? These five cohorts comprise the individual patient data meta-analysis (IPDMA).
2. What are the estimated five-year risks of first and second ICH or FND, definitely or possibly due to CCM:
    a. in the two Scottish cohorts?
    b. in the five cohorts forming the IPDMA?
3. Which baseline characteristics are associated with the risk of ICH or FND occurring within five years of CCM diagnosis:
    a. in the two Scottish cohorts?
    b. in the five cohorts forming the IPDMA?
4. Over the course of five years, from the time of first clinical event, how does the level of dependence compare for adults who have experienced a single clinical event (ICH or FND) and those who have suffered a recurrence?
5. How does the functional outcome of adults diagnosed with CCM who have undergone interventional treatment compare with those who have been managed conservatively?
6. Is it possible to predict, at the time of diagnosis, an individual's risk of a subsequent ICH or FND, assuming no interventional treatment is performed in the intervening period?

The thesis is arranged in the following order. First, a brief description of CCM is given in Chapter 2, and the level of knowledge pertaining to haemorrhage or focal neurological deficit in CCM at the beginning of this research project is outlined in a short literature review (Chapter 3).

In Chapter 4, data from adults diagnosed with cerebral cavernous malformation in the Scottish Intracranial Vascular Malformation Study (SIVMS) will be analysed; the risks of a first and recurrent ICH (and the composite outcome of ICH or FND) over five years of untreated follow-up will be estimated, and the functional outcome of adults who have suffered at least one ICH or FND will be examined. In Chapter 5, there is a slight change of focus: using the data from the first cohort of SIVMS, the functional and clinical outcomes of those who received interventional treatment are compared with those who were conservatively managed.

In the next four chapters, the focus reverts to the untreated clinical course. The prognosis for CCM appears to be comparatively benign and clinical outcome events are not plentiful, which is of course very good news for the patient, albeit less good for the statistician. In an attempt to increase the number of outcome events, to enable identification of risk factors associated with ICH or FND in untreated follow-up, and the construction of a prognostic model, three other research centres agreed to collaborate and contribute data. Thus in Chapters 6–9, the individual patient data meta-analysis and subsequent prognostic models are described, together with a subsidiary analysis of whether sex has an effect on recurrent ICH (or a second ICH or FND). In the final chapter (Chapter 10), the main strands of the thesis are discussed and suggestions are made for the direction that future research on this condition should take.

The statistical analyses reported in this thesis were performed using IBM SPSS Statistics for Windows, versions 19.0 and 21.0 (Armonk, NY: IBM Corp), and Stata IC 12 (4905 Lakeway Drive, College Station, Texas 77845).

# Chapter 2: Clinical background

Although cerebral cavernous malformations (CCM) have been recognized as a clinical condition since at least the middle of the nineteenth century, when Rudolf Virchow, the German pathologist, described it in 1863 (Bertalanffy et al., 2002), until the mid-1980s they could only be diagnosed conclusively either after surgery or at autopsy. Because CCMs cannot be visualized on angiograms, due to the very slow blood flow, they were often described as angiographically occult vascular malformations (AOVMs) or cryptic vascular malformations (Batra et al., 2009, Kim et al., 1997). However, the incidence of cavernous malformations has dramatically increased since the 1990s, with the widespread availability and usage of magnetic resonance imaging (MRI). The estimated annual CCM detection rate in Scotland was 0.56 (95% confidence interval 0.41 to 0.75) per 100,000 from 1999 to 2000 (Al-Shahi Salman et al., 2012), and 0.78 (95% CI 0.67 to 0.90) per 100,000 between 2006 and 2010. The results of a study investigating incidental findings on brain MRI suggest a CCM prevalence of one in 625 neurologically asymptomatic adults (Morris et al., 2009).

## 2.1 Pathology

Cerebral cavernous malformations, also known as cavernomas, cavernous angiomas or cavernous haemangiomas, are the second most common type of intracranial vascular malformation (IVM) and account for about 5–15% of all IVMs (Maraire and Awad, 1995, Moriarity et al., 1999, Batra et al., 2009, Abla et al., 2011, Engelmann et al., 2011, Berg and Vay, 2011). A CCM is a small round cluster of thin-walled, dilated

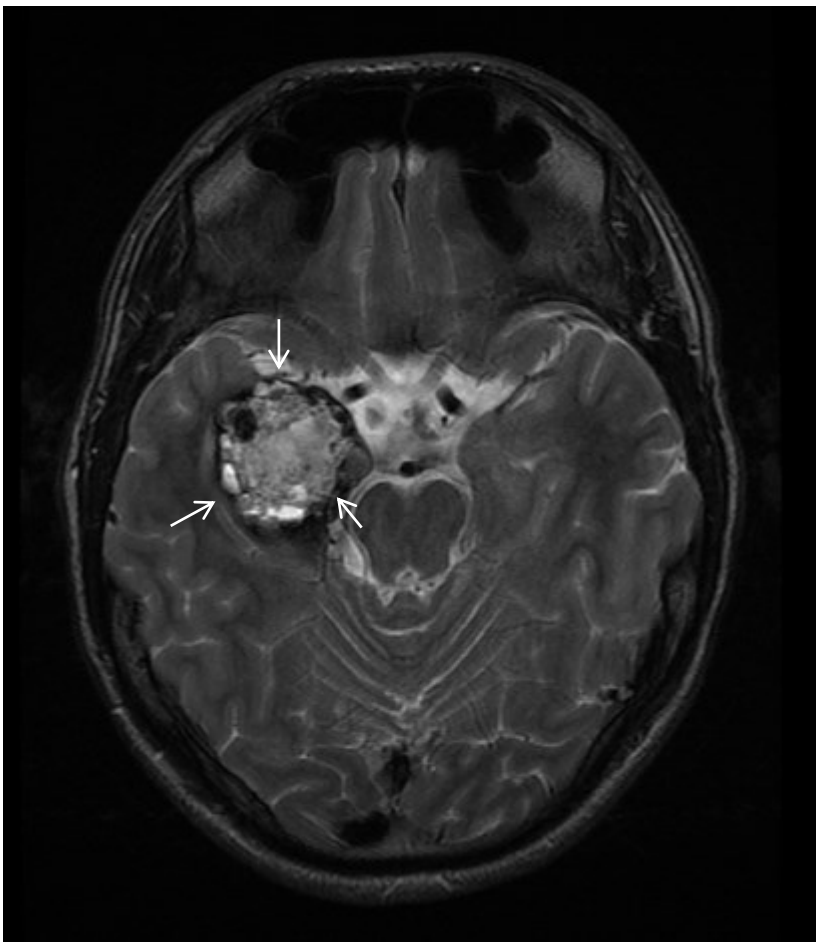


**Figure 2.1 Cerebral cavernous malformation**

abnormal blood vessels, packed together with no intervening brain tissue (Figure 2.1). Visually, the CCM is multi-lobulated and resembles a raspberry.

The blood vessels in cavernous malformations are lined with a single endothelial cell layer in a similar manner to capillaries: there are no elastic or smooth muscle fibres in the vascular walls, and astrocytic endfeet are also absent (Kuker and Forsting, 2008, Batra et al., 2009, Batra et al., 2011, Bertalanffy et al., 2002). There is a slow flow of blood in the lesion with leaky junctions between the cells. The brain area surrounding the CCM often has haemosiderin staining, where small quantities of blood may have previously oozed out, since the structure of CCM blood vessels lacks the morphological basis of the blood–brain barrier. Calcification can also occur within the walls of the blood vessels and within the adjacent brain tissue (Batra et al., 2011); this

tends to be more common in people presenting with a seizure, and rarer in someone presenting with an intracranial haemorrhage.

## 2.2 Characteristics of cavernous malformations

The disease can take two different forms: sporadic or familial. The former is characterized by the presence of a single, non-hereditary lesion and is the more common. Characteristics of the familial form include a higher prevalence of multiple lesions (50-84% in familial cases compared with less than 33% in sporadic cases) and also the appearance of de novo lesions (Maraire and Awad, 1995, Zabramski et al., 1994). There is an autosomal dominant pattern of inheritance, and two genes on chromosome 7 and one on chromosome 3 have been discovered to be abnormal (Labauge et al., 2001).

However, in this thesis, no distinction is made between the sporadic and familial form of the disease, and adults with either form are included in the analysis. There are several reasons for adopting this approach: CCM is not a common disease and there was a reluctance to reduce the number of people included in the study by subdividing the population into two unequal-sized groups, given that there is no evidence to date to suggest that the risk of a haemorrhage differs between the two forms of the disease. It would also be challenging to identify accurately all adults in the cohorts who had the familial form since genetic testing would be required, which in many diagnoses (for example, an elderly patient who has been diagnosed incidentally) would be inappropriate.

Historically, cavernous malformations were believed to be congenital lesions. In 1994, however, Zabramski and colleagues reported that six of 21 patients in their study of the familial form of the disease had developed 17 new lesions that had not been visualized on earlier MRI (Zabramski et al., 1994). There have also been reports of appearances of de novo lesions following intracranial radiation, especially in children (Pozzati et al., 1996) and after viral infection. Thus it is now recognized that CCMs

are dynamic lesions: they can increase or diminish in size over time as well as appear de novo (Clatterbuck et al., 2000, Nimjee et al., 2006). Since clinicians in Scotland tend not to perform neuro-imaging routinely, unless a patient's symptoms suggest that he/she would benefit from another scan, it is not possible to investigate whether individual lesions have increased or diminished in size over time in the Scottish cohorts described in this thesis.

Cerebral cavernous malformations may be located in any region of the brain; the majority tend to be supratentorial, distributed in a similar proportion to neural tissue (Batra et al., 2009). There is, however, a possibility that the area of the brain in which a CCM is situated may play a part in determining the problems the CCM causes. For example, in the brainstem the neural functions are tightly packed; thus CCMs located there are adjacent to eloquent areas of the brain and so can do more damage than when they are located in other, non-eloquent areas of the brain.

Patients can present with a variety of symptoms, the most common of which are epileptic seizure, intracranial haemorrhage (ICH), focal neurological deficit (FND), headache or tinnitus. Since the advent of high-resolution MRI, however, an increasing number of patients have been presenting asymptomatically (Morris et al., 2009): a brain scan has been performed for some other reason (for example, traumatic brain injury) and the radiologist has also observed one (or more) incidental CCMs. In addition, sometimes a patient's symptoms can only possibly (but not definitely) be attributed to the CCM. In both these cases, the presentation is described as 'incidental'.

The ability to detect the presence of asymptomatic CCMs using high-resolution MRI has led to the screening of other family members, if they so wish, when a patient has been diagnosed with the familial form of the disease; this practice also contributes to the large number of people with cavernous malformations presenting incidentally. As more people receive a CCM diagnosis incidentally, it is even more important to understand the untreated clinical course of the disease, since it informs decisions on how best the condition should be managed.

Cavernous malformations can vary in size from a few millimetres width to 4 centi-metres or more. Occasionally they are found in conjunction with developmental

venous anomalies (DVA) (or venous malformations) (Abdulrauf et al., 1999), although it is not unusual for the latter to be radiographically occult and only be discovered during surgery (Rigamonti et al., 1988, Porter et al., 1997, Abdulrauf et al., 1999).

## 2.3 Problems associated with CCM

### 2.3.1 Seizure

Epileptic seizure is the most common form of symptomatic CCM presentation; patients who present with a seizure tend to be younger (under 40 years), are more likely to be male, and their cavernomas are located supratentorially. If a lesion has become epileptogenic, then the risk of seizures will continue, unless the cavernoma is surgically removed; thus patients will require lifelong anti-epileptic therapy (Bergey, 2011, Josephson et al., 2011).

However, the occurrence of seizures and epilepsy during follow-up is not explored in this thesis; adults who have undergone interventional treatment as a result of epilepsy are included in the treated group in Chapter 5 and the subsection on informative censoring in Chapter 8 below.

### 2.3.2 Haemorrhage and focal neurological deficit

As a result of their angioarchitecture, CCM are prone to bleed. Although the quantity of blood leaking out tends to be small because the blood flow is very slow, even a small ICH can result in a clinically significant neurological deficit (Aiba et al., 1995), especially when the CCM is located in the brainstem or another eloquent area.

A major aim of this thesis is to investigate the risk of haemorrhage in adults who have been diagnosed with a CCM, whether they have a non-haemorrhagic or a haemorrhagic presentation. However, investigating haemorrhage from cerebral cavernous malformations is not without its challenges. In the past, different researchers

have used different definitions of haemorrhage and different starting points. Furthermore, visualization of blood on imaging requires different radiographic modalities at different time points. In addition, clinical practice and the quirks of human behaviour add to the challenge.

## Definition of haemorrhage

Since CCM contain blood products at various stages of evolution, it is crucial to define the term 'haemorrhage' to avoid confusion (Porter et al., 1997, Kuker and Forsting, 2008). The definition of symptomatic haemorrhage used throughout this thesis is that agreed in 2008, at a scientific workshop of the Angioma Alliance, and reproduced below:

> A clinical event involving both:
>
> > Acute or subacute onset symptoms (any of headache, epileptic seizure, impaired consciousness, new/worsened focal neurological deficit referable to the anatomic location of the CM).
> >
> > Radiological, pathological, surgical, or rarely only cerebrospinal fluid evidence of recent extra- or intralesional haemorrhage.
>
> The mere existence of a hemosiderin halo, or solely an increase in CM diameter without other evidence of recent haemorrhage, are not considered to constitute haemorrhage. (Al-Shahi Salman et al., 2008)

## Radiological considerations

The appropriate neuro-imaging modality used to detect blood depends upon when the suspected haemorrhage occurred. Ideally, a CT scan should be performed within a week of the suspected haemorrhage for the blood to be visualized; older haemorrhages are visible on MRI for between two weeks and up to two or three months after the event. If possible, the MRI should be compared with one performed earlier, which does not show the abnormalities, or one taken at a later date, when the haemorrhage

has evolved further. Occasionally a CCM can be partially or completely obscured by a haemorrhage on MRI or, conversely, an ICH can obscure a CCM; therefore repeat scanning several months later, when the haemorrhage has broken down into its constituent parts, is desirable (Josephson and Al-Shahi Salman, 2011).

## Focal neurological deficits

### *Definitions*

A non-haemorrhagic focal neurological deficit (NH-FND) is defined as 'a new or worsened focal neurological deficit referable to the anatomic location of the CCM, which may present with other clinical features of intracranial haemorrhage, but without evidence of recent blood on timely brain imaging or pathological examination, or examination of the CSF' (cerebrospinal fluid) (Al-Shahi Salman et al., 2008).

Focal neurological deficit not otherwise specified (NOS-FND) is defined as a non-haemorrhagic FND 'where pathological investigation, CSF examination, or timely imaging have not been performed at all or at the correct time to establish whether haemorrhage, edema, or lesion growth underlie the clinical deterioration' (Al-Shahi Salman et al., 2008).

### *Potential haemorrhages*

The challenge of trying to understand and estimate the risk of haemorrhage for adults diagnosed with CCM is compounded by various scenarios in clinical practice that can result in the misclassification of a true haemorrhage as a focal neurological deficit. For example, patients with cavernous malformations tend to have milder deficits than people with, for example, arteriovenous malformations, because less blood is lost, as CCMs have low pressure and slow blood flow (El-Koussy et al., 2011). Thus reporting bias and investigation bias may lead to an underestimation of ICH: a patient may delay reporting seemingly minor symptoms to their general practitioner, who in turn may be slow to investigate because the symptoms seem mild, and the patient is known to have a CCM, but is being managed conservatively. As a result, the appropriate neuro-

imaging will not be performed at the appropriate time, or possibly at all, and the condition will be described in the patient's notes as a focal neurological deficit, when it is in fact a symptomatic intracranial haemorrhage (Josephson and Al-Shahi Salman, 2011).

On the other hand, CCM diagnosis itself may be subject to detection bias, since it relies on brain imaging of the right type being performed at the right time. Clinicians tend to investigate the cause of ICH symptoms in young, normotensive adults, whereas these symptoms in older, hypertensive adults are less likely to be further investigated, regardless of whether the individuals are known to harbour a cavernoma.

Thus some NOS-FNDs are in fact ICH, but without the timely neuro-imaging to confirm the blood, and therefore the incidence of haemorrhage in people with cavernous malformations is likely to be underestimated. For this reason, reporting standards recommend combining proven ICH and FND into a composite outcome (referred to as 'clinical event' throughout this thesis).

# Chapter 3: Literature review

## 3.1 Introduction

As was described in Chapter 2 above, although cerebral cavernous malformations have existed in the past, it is only since the advent and widespread usage of MRI that their conclusive diagnosis has been possible on a large scale. Before the invention of MRI, CCM could be diagnosed only after surgical excision of the lesion or at pathological examination during autopsy. Therefore before 1990 the disease literature was restricted to a very few CCM case studies; after this date, interest in the disease increased dramatically and a number of papers were published, although many of these concentrated on a description either of the different forms of interventional treatment or of the molecular structure of the disease, rather than the clinical course of the untreated disease.

With the increase in detection of incidental lesions due to the widespread use of MRI, however, it has become imperative for clinicians to understand the natural history of the condition so that they are able to determine the optimum treatment for individual patients (Engelmann et al., 2011). Thus a number of seminal studies were published in the 1990s and early 2000s, describing the natural history of the condition and examining haemorrhage or focal neurological deficit and seizure rates. In this thesis, however, interest is confined to haemorrhage or focal neurological deficit in the untreated course of cerebral cavernous malformations.

## 3.2 Method

A systematic search of the literature was carried out for reports of the risk of ICH or FND (or subsequent ICH or FND) in untreated follow-up among adults whose CCM diagnosis was validated by brain MRI or pathological examination. Two online databases were searched – Embase, the Excerpta Medica database, and Medline, the National Library of Medicine database – from 1980 to August 2011 (see Table 3.1). The searches were limited to English or French language publications, and specific to human adults.

Criteria for a study to be included in this literature review were for the sample size to be at least 20 patients (to avoid individual case studies); the period during which the patient was at risk of haemorrhage was to be calculated from the time of first presentation or CCM diagnosis, not from birth; and ICH was to be clearly defined. Other desirable study characteristics included a definite diagnosis of CCM after radiological or pathological examination; a specific inception point, i.e. some distinct time-point during the course of the disease, at which patients were recruited into the cohort; prospective data collection; a population-based sample in preference to a hospital-based one; objective pre-defined clinical outcome events to include mortality, ICH and a standard measure of functional outcome (for example, the modified Rankin scale); and patients to be assessed blind by clinicians to the prognostic factors of interest.

The title of every publication identified by the electronic searches was read, and where the title appeared to be relevant to this study, abstracts were examined to ascertain how many of the above criteria were met. In addition, reference lists in selected papers published after 2000 were checked to discover other, more recent papers cited in them.

## 3.3 Results

In the Embase and Medline searches, after the language and human adult limits were set, 505 and 366 publications were identified respectively. After combining these two results, 152 duplicate records were removed, and 513 records were excluded for the following reasons: irrelevance, case reports, children or the study was too small (less than 20 adults) (see Figure 3.1). Of the 206 records remaining, 123 were eligible to be included in the literature review. The criterion that the period during which the patient was at risk of haemorrhage was to be calculated from the time of first presentation or CCM diagnosis, not from birth, had to be relaxed, however, as almost all studies used the 'lifetime method' of calculating the risk of ICH.

In the literature review that follows, the main published studies have been critically appraised, and some of the seminal papers have been described in greater detail; the salient points are summarized in section 3.4.

### 3.3.1 Critical appraisal of the literature

Of the 21 seminal studies identified in the search, fourteen were retrospective, based at one or two hospitals or neurological/neurosurgery referral centres; researchers reviewed all the radiological images of the brain that had been performed within a defined period of time at the particular institution, or possibly one or two other collaborating centres, to identify all potential cerebral cavernous malformations. Clinical records were then examined retrospectively for all patients who were suspected of harbouring a CCM, and the patients were contacted for further follow-up. Researchers were predominantly interested in the prevalence of the disease and the number of haemorrhages in follow-up; tentative suggestions were made of any potential risk factors that might have been observed in their particular cohort.

**Table 3.1 Literature search strategies**

**Embase**

| | |
|---|---|
| 1. | Brain Hemangioma/ |
| 2. | brain ventricle cavernoma/ |
| 3. | cavernous hemangioma/ |
| 4. | (cavernous adj5 (angioma$ or hemangioma$ or malformation$)).tw. |
| 5. | cavernoma$.tw. |
| 6. | 3 or 4 or 5 |
| 7. | central nervous system/ or exp brain/ or exp brain ventricle/ or exp brain artery/ |
| 8. | exp brain tumor/ |
| 9. | (brain$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial).tw. |
| 10. | 7 or 8 or 9 |
| 11. | 6 and 10 |
| 12. | 1 or 2 or 11 |
| 13. | exp brain haemorrhage/ |
| 14. | exp bleeding/ |
| 15. | 13 or 14 |
| 16. | 12 and 15 |

**Medline**

| | |
|---|---|
| 1. | Hemangioma, Cavernous, Central Nervous System/ |
| 2. | Hemangioma, Cavernous/ |
| 3. | (cavernous adj5 (angioma$ or hemangioma$ or malformation$)).tw. |
| 4. | cavernoma$.tw. |
| 5. | 2 or 3 or 4 |
| 6. | exp brain/ or central nervous system/ or exp cerebral arteries/ |
| 7. | Exp brain neoplasms/ |
| 8. | (brain$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial).tw. |
| 9. | 6 or 7 or 8 |
| 10. | 5 and 9 |
| 11. | 1 or 10 |
| 12. | exp Hemorrhage/ or exp Intracranial Hemorrhages/ |
| 13. | Focal neurological deficit$.tw. |
| 14. | 12 or 13 |
| 15. | 11 and 14 |

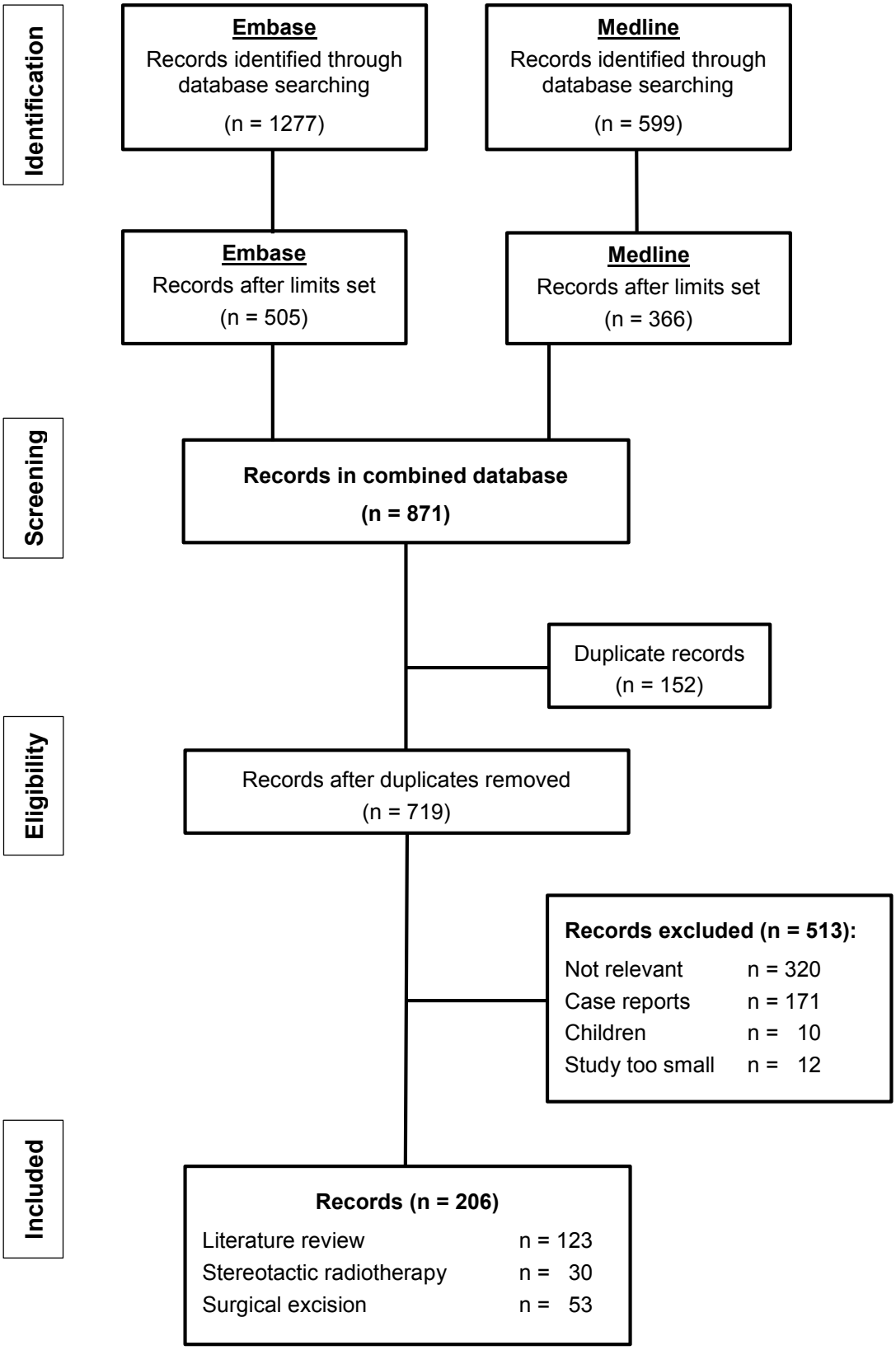



**Figure 3.1 Flowchart of database searches for literature review**

Unfortunately many of these studies suffered from one or more of the following problems. In retrospective studies, the number of patients lost to follow-up is likely to be greater than in prospective studies, and in some cases the length of follow-up was only a matter of months, which was too short a time-period for subsequent clinical events to occur. As several researchers have noted previously, in many cases there was no defined inception point, and definitions of haemorrhage were frequently vague (Feiz-Erfan et al., 2002, Kuker and Forsting, 2008, Josephson and Al-Shahi Salman, 2011). Additionally, very few studies gave any indication of patient functional outcome or level of dependence at the end of the study period; ideally, this should be assessed by someone who is blinded to the prognostic features of the study, and a standardized disability scale should be used (Josephson and Al-Shahi Salman, 2011).

In several studies, it was assumed that lesions were congenital and haemorrhage rates were calculated on the basis of lifetime risk; it is now known that CCMs are dynamic lesions and using the lifetime-risk method seriously underestimates the haemorrhage rate. Even where a prospective haemorrhage rate was calculated, some studies used the total number of haemorrhages during follow-up, rather than either using the first haemorrhage, or distinguishing between a first and recurrent bleed; including all haemorrhages that occurred during follow-up overestimates the risk of an individual suffering one or more haemorrhage. Differing haemorrhage rates can sometimes be explained by the fact that patients with CCMs may have been managed conservatively in one institution for a number of years, but have then been transferred to the study centre – a tertiary specialist centre – on clinical deterioration; hence the requirement for a specific inception point that refers to the progress of the disease, such as the date of first CCM diagnosis.

Some studies reported haemorrhage rates in terms of patient-years, whereas others used lesion-years, and this makes comparison of rates between different studies more problematic, if not impossible. In addition, most studies did not account for patients who suffered focal neurological deficits (FNDs), which are an important cause of morbidity, particularly as occasionally FNDs may in reality be instances of ICH, but cannot be so defined because brain imaging may not have been performed at the appropriate time with the appropriate modality to detect blood on the scan (Josephson

and Al-Shahi Salman, 2011) (see subsection 2.3.2 above). Several of the studies focused on a specific patient population (for example, familial CCMs or brainstem CCMs), so the haemorrhage rates in different studies may not be directly comparable.

Moreover, it is not possible to compute an accurate detection rate from these studies, because the initial populations consisted either of hospital patients or patients who had been referred to a large tertiary specialist centre. Thus patients from neither group were representative of the general population, as they had all been referred to a medical establishment; any detection rate calculated from these studies would be subject to selection bias, and the rate of CCM in the general population would be overestimated, because the initial population did not include healthy subjects (Feiz-Erfan et al., 2002).

In addition, it is likely that many studies suffered from referral bias: those adults who were referred to a tertiary specialist centre and who provided the data for some of the studies of the untreated clinical course of the disease will have a poorer prognosis than those who were diagnosed with CCM, but were not referred to such a centre (Al-Shahi and Warlow, 1999). For this reason, further studies using prospective population-based cohorts (such as the Scottish Intracranial Vascular Malformations Study (SIVMS), http://www.saivms.scot.nhs.uk/, described in Chapter 4 below) are crucial. Moreover, in population-based studies, mortality data will be more complete, since participants who die in the community, rather than in a medical establishment, will be recorded, whereas these community deaths will not be included in hospital-based studies; therefore hospital-based studies will arguably present an over-optimistic prognosis with regard to CCM mortality (Al-Shahi and Warlow, 1999).

There is also the possibility of treatment bias in hospital-based studies. Individuals with more severe symptoms tend to be referred to a tertiary referral centre, where surgeons may be more likely to operate at an earlier phase in the disease, thereby reducing the length of conservative-management period, and thus the untreated time available for an event to occur.

Nonetheless, to give an approximation of the scale of CCM incidence, several authors reviewed all MRI scans in their institution over a set period of time. Robinson and

colleagues found 66 patients with CCMs from 14,035 consecutive MRI reports, giving an incidence of 4.7 per 1,000 patients (Robinson et al., 1991), and Del Curling found 32 subjects from 8,131 consecutive MRI reports, with a corresponding incidence of 3.9 per 1,000 (Del Curling et al., 1991). These estimates are similar to the 3.9 per 1,000 and 5.3 per 1,000 from two earlier autopsy studies ($n$ = 4,000 and 24,535 respectively) (Sarwar and McCormick, 1978, Otten et al., 1989). More recently, El-Koussy and colleagues have reported 'an annual incidence of 1.31 and 0.55 newly diagnosed symptomatic and asymptomatic cases respectively per 100,000 inhabitants' in the canton of Bern (El-Koussy et al., 2011), although the authors qualify this by adding that it is possible that some patients from other regions of Switzerland may be included in this rate.

## Review of published studies

Bearing in mind the potential problems described above, the studies cited below do give a useful insight into the condition and the most pertinent points are summarized below (see Tables 3.2 and 3.3 below).

The average age at presentation leading to a CCM diagnosis was 31–42 years, although in Zabramski's study on familial CCMs the average age was 25 years (Zabramski et al., 1994), as asymptomatic family members across the generations were also screened. The modes of presentation in the non-specialized studies were in the following ranges: ICH (9–56%), seizure (22–52%), FND (8–46%) and incidental (12–21%). However, these studies were based on data derived in the 1980s and 1990s for the most part; the percentage of patients presenting incidentally is likely to be greater since then, as the availability and usage of MRI has increased considerably. In the two Scottish cohorts, recruited between 1999 and 2010, the percentage of adults presenting incidentally was 46% and 41% (see Tables 4.3–4.5 below). Supratentorial lesions tended to be more common (50–86%) than infratentorial lesions.

**Table 3.2 Summary of baseline characteristics in published studies**

| Study | Recruitment | Age (years) | | Female | Presenting symptoms (%) | | | | | CM location (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | mean | range | (%) | ICH | S | FND | H | I | Supra | Infra |
| Curling et al (1991) | Bowman Gray School of Medicine, NC | 37.6[a] | 16–72[a] | 47 | 9 | 50 | 22 | 34 | 19 | 72[b] | 16[b] |
| Robinson et al (1991) | Cleveland Clinic Foundation, OH | 34.6 | 0–84 | 45 | 9 | 52 | 45 | 30 | 14 | 84 | 16 |
| Fritschi et al (1994) | Bern, CH + Barrow NI + literature | 31.8 | 2–69 | 51 | — | — | — | — | 0 | 0 | 100 |
| Zabramski et al (1994) | Barrow Neurological Institute, Phoenix, AZ | 25 | 7–51 | 58 | — | 39 | — | 52 | 39 | 92 | 8 |
| Aiba et al (1995) | Niigata University, Japan | — | — | 46 | 56 | 23 | — | — | 21 | 66 | 34 |
| Kondziolka et al (1995) | University of Pittsburgh, PA | 37.3 | 4–82 | 51 | 50 | 23 | — | 15 | — | 48 | 52 |
| Kim et al (1997) | Yonsei University Coll. of Medicine, Seoul | 32.2 | 4–63 | 39 | | 41 | 8 | 6 | 12 | 69 | 31 |
| Porter et al (1997) | University of Toronto VM Study Group | 37.5 | — | 49 | 25 | 36 | 20 | 6 | 12 | 64 | 36 |
| Abdulrauf et al. (1999) | Yale University School of Medicine | 31.6 | 4–70 | — | 44 | 22 | 20 | 0 | 15 | 64 | 36 |
| Moriarity et al (1999) | Johns Hopkins Hospital, Baltimore, MD | 34.6 | 7–78 | 65 | 13 | 49 | 46 | 65 | 2 | 81 | 19 |
| Porter et al (1999) | Barrow Neurological Institute, Phoenix, AZ | 37 | 3–64 | 62 | 97 | — | — | — | 3 | 0 | 100 |
| Barker et al (2001) | Massachusetts General Hospital, Boston | 35* | 4–63 | 56 | 100 | — | — | — | — | 50 | 50 |
| Kupersmith et al (2001) | Beth Israel Medical Center, NYC | 37.5 | 6–73 | 59 | 73 | — | — | 43 | — | 0 | 100 |
| Labauge et al (2001) | INSERM, Paris | 40.8 | 13–65 | 58 | 0 | 0 | 0 | 0 | 100 | 86 | 14 |
| Hasegawa et al (2002) | University of Pittsburgh, PA | 37.7 | 4–81 | 44 | 100 | — | — | — | 0 | 21 | 79 |
| Mathiesen et al (2003) | Karolinska Institute, Stockholm | — | — | — | — | — | — | — | 19 | 0 | 100 |
| Wang et al (2003) | Beijing Neurosurgical Institute, Beijing | 33.5 | 3–70 | 42 | 100 | — | — | — | 0 | 0 | 100 |
| Ghannane et al (2007) | Clermont-Ferrand, France | 40.1 | 7–78 | 51 | 0 | 32 | 38 | 30 | 19 | 56 | 28 |
| Tarnaris et al (2008) | National Hospital for Neurology, London | 36.8 | — | 67 | 57 | 0 | 24 | — | 19[c] | 0 | 100 |
| Hauck et al (2009) | Southwestern Medical Center, Dallas, TX | 37.5 | 10–77 | 68 | — | — | — | — | 0 | 0 | 100[d] |
| Abla et al (2011) | Barrow Neurological Institute, Phoenix, AZ | 41.8 | 19–77 | 60 | 97 | — | 2.7 | — | 0.4 | 0 | 100 |

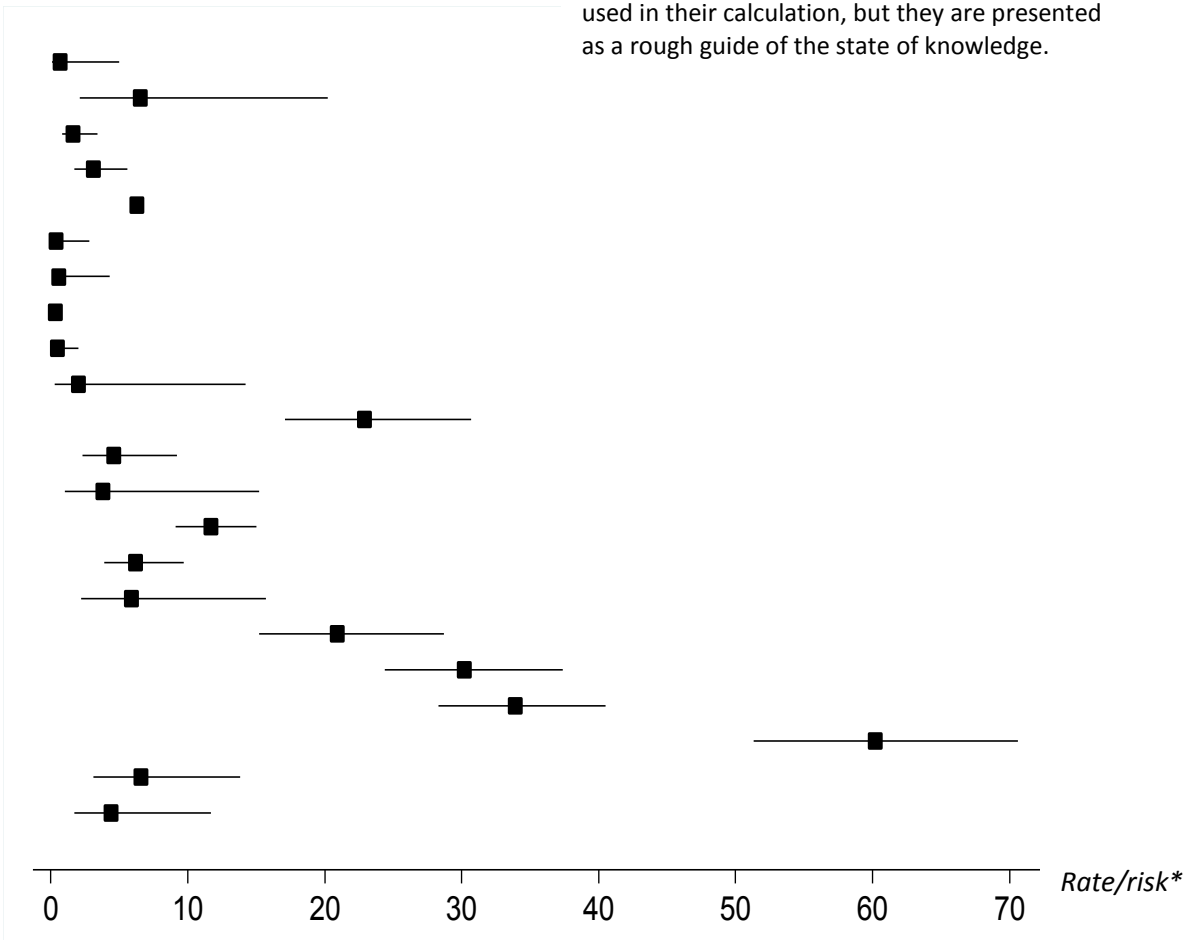
Notes
ICH intracranial haemorrhage; S seizure; FND focal neurological deficit; H headache; I incidental; supra supratentorial; infra infratentorial. * Median.
[a] Age at last contact
[b] 12% had multiple CCMs located in both areas.
[c] Includes patients who presented with initial episode of ICH from CCM not in brainstem.
[d] 43 superficial location; 3 deep location.

**Table 3.3 Summary of initial haemorrhage and re-haemorrhage rates in published studies**

| Study | Study type | Selection criteria | Patient source | Number of patients | Follow-up (yrs) mean | Follow-up (yrs) range | 1st haemorrhage rate | Re-haemorrhage rate |
|---|---|---|---|---|---|---|---|---|
| Curling et al (1991) | R | | 1 H | 32 | – | – | 0.3% per person-year | |
| Robinson et al (1991) | R | | 1 H | 66 | 2.2 | – | | 0.7% per lesion-year |
| Fritschi et al (1994) | R | brainstem | 2 N + L | 41 + 98 | 2.5 | 0–32 | 2.7% per lesion-year | 21% per lesion-year |
| Zabramski et al (1994) | P | familial | 1 N | 21 | 2.2 | 1–5.5 | - | 6.5% per patient-year |
| Aiba et al (1995) | R | | 1 N | 110 | 4.7 | – | 0.4% per patient-year | 22.9% per lesion-year |
| Kondziolka et al (1995) | R + P | conservative management | 1 N | 122 | 2.8 | 0.1–6.8 | 0.6% per patient-year<br>2.4% per patient-year[a] | 4.5% per patient-year<br>5.0% per patient-year[a] |
| Kim et al (1997) | R | | 1 H | 62 | 1.9 | 1–4 | 2.3% per patient-year | 3.8% per patient-year |
| Porter et al (1997) | R + P | | 1 IVM | 110 | 3.8 | – | | |
| Abdulrauf et al. (1999) | R | | 1 N | 55 | – | – | | |
| Moriarity et al (1999) | P | | 1 N | 68 | 5.2 | – | 3.1% per patient-year | |
| Porter et al (1999) | R | brainstem | 1 N | 100 | 2.9 | – | - | 30.2% per patient-year |
| Barker et al (2001) | R | bled at presentation | 1 N | 136 | 3.8 | – | - | 14% per patient-year |
| Kupersmith et al (2001) | R | brainstem | 1 NO | 37 | 4.9 | 0.2–23 | | |
| Labauge et al (2001) | P | asymptomatic familial | MC | 33 | 2.1 | 0.5–4.5 | 4.3% per patient-year | - |
| Hasegawa et al (2002) | R + P | bled at presentation[b] | 1 RS | 82 | 4.3 | 0.2–18 | - | 33.9% per patient-year |
| Mathiesen et al (2003) | R + P | brainstem + deep | 1 N | 68 | 4.6 | – | 2% per patient-year | 7% per patient-year |
| Wang et al (2003) | R | brainstem | 1 N | 137 | 1.8 | 0.5–11 | 6% per patient-year | 60% per patient-year |
| Ghannane et al (2007) | R | | 1 N | 79 *total*<br>39 *cons. man.* | 3.4<br>2.5 | <br>0.7–9 | 0.01% per patient-year | 6.27% per patient-year |
| Tarnaris et al (2008) | R | brainstem | 1 N | 21 | 6.6 | 0.5–20 | - | 5% per patient-year |
| Hauck et al (2009) | R | symptomatic brainstem | 1 N | 44 | 0.3 | 0–8 | - | 42% per patient-year |
| Abla et al (2011) | R | brainstem, surgical | 1 N | 260 | 4.3 | 0–37 | - | 35% per patient-year |

**Notes**
R retrospective study; P prospective study;
H hospital; IVM IVM study group referral unit; L literature; MC multicentre; N neurosurgery unit; NO neuro-ophthalmology unit;
RS radiosurgery unit
[a] brainstem CCM; [b] mostly brainstem CCMs.

| Study | Selection criteria | Sample size |
|---|---|---|
| ***First/recurrent ICH not distinguished*** | | |
| Robinson *et al*., 1991 | None | 66 |
| Zabramski *et al*., 1994 | Familial | 21 |
| Porter *et al*., 1997 | None | 110 |
| Moriarity *et al*., 1999 | None | 68 |
| Ghannane *et al*., 2007 | None | 39 |
| ***First ICH*** | | |
| Aiba *et al*., 1995 | None | 48 |
| Kondziolka *et al*., 1995 | None | 61 |
| Flemming *et al*., 2012 | None | 174 |
| Al-Shahi Salman *et al*., 2012 | None | 96 |
| Mathiesen *et al*., 2003 | Brainstem + deep | 11 |
| ***Recurrent ICH*** | | |
| Aiba *et al*., 1995 | None | 62 |
| Kondziolka *et al*., 1995 | None | 61 |
| Kim *et al*., 1995 | None | 28 |
| Barker *et al*., 2001 | None | 136 |
| Flemming *et al*., 2012 | None | 74 |
| Al-Shahi Salman *et al*., 2012 | None | 18 |
| Fritschi *et al*., 1994 | Brainstem | 101 |
| Porter *et al*., 1999 | Brainstem | 100 |
| Hasegawa *et al*., 2002 | Brainstem | 83 |
| Wang *et al*., 2003 | Brainstem | 137 |
| Mathiesen *et al*., 2003 | Brainstem + deep | 23 |
| Tarnaris *et al*., 2008 | Brainstem | 21 |




***Note***
The rates and risks in this figure are as reported in the literature; inconsistent methods were used in their calculation, but they are presented as a rough guide of the state of knowledge.

**Figure 3.2 Symptomatic intracranial haemorrhage rates during follow-up in studies of the untreated clinical course of participants diagnosed with cerebral cavernous malformations (point estimates and 95% confidence intervals)**

Del Curling and colleagues conducted a retrospective study, reviewing all the MRI scans from the North Carolina Baptist Hospital between 1986 and 1989. From 8,131 images, 32 patients (with 76 lesions) fulfilled their criteria for CCM diagnosis (Del Curling et al., 1991); 23 (72%) had supratentorial location, five (16%) infratentorial, and four (12%) had lesions in both locations. Only three patients had sustained a prior haemorrhage, and the haemorrhage rate was thus calculated as 0.25% per person-year of exposure or 0.1% per lesion per year, using the lifetime-risk method. They concluded that cerebral cavernous malformations were more common than had previously been believed, but recommended that the risks and benefits of surgery be carefully assessed for each patient before surgical excision, as the risk of haemorrhage was low in these patients; they also advocated that a large prospective study be undertaken to examine the natural history and management of the disease.

In a similar retrospective study ($n$ = 66), Robinson and colleagues at the Cleveland Clinic Foundation in Ohio reviewed 14,035 consecutive MRI scans performed there between 1984 and 1989. They reported six people presenting with haemorrhage, and a single haemorrhage occurring in 143 lesion-years of follow-up; 86% of the adults who had experienced a haemorrhage ($n$ = 7) were women, and the researchers calculated a haemorrhage rate during follow-up of 0.7% per lesion per year (Robinson et al., 1991). They noted that patients with infratentorial lesions were more likely to present with FND ($p$ = 0.006), whereas those with supratentorial lesions were more likely to present with seizure ($p$ = 0.005).

In a prospective study of 68 patients (44 of whom were female), followed between 1987 and 1996 at the Johns Hopkins Hospital, Baltimore, Moriarity and colleagues also noted that patients with supratentorial lesions were more likely to present with seizure. They calculated an overall ICH rate of 3.1% per patient-year, and argued that prior haemorrhage was not a risk factor for ICH in follow-up (of mean duration 5.2 years), as none of the patients who sustained an ICH in follow-up presented with an ICH (Moriarity et al., 1999). In addition, female patients had a significantly higher prospective ICH rate (4.2% per patient-year, compared with 0.9% per patient-year for men). They concluded that despite the fact that the surgical patients in their series had a good outcome, asymptomatic lesions are best managed conservatively.

At the University of Pittsburgh, in Pennsylvania, Kondziolka et al. prospectively followed 122 patients whose CCM was visualized on MRI between 1987 and 1993, and in whom conservative management was recommended, for a mean of 34 months (Kondziolka et al., 1995). In this cohort, 50% had experienced at least one prior haemorrhage, and 52% of lesions were located in the brainstem, basal ganglia or thalamus. The prospective haemorrhage rate in those who had not previously sustained a haemorrhage was 0.6% per patient-year, and the prospective re-haemorrhage rate was 4.5% per patient-year, demonstrating the fact that once a lesion has bled, the probability of experiencing a re-bleed is greatly increased. They found no significant difference in haemorrhage rate for men and women, by lesion location, or between patients with or without seizures, or between subjects with solitary or multiple lesions (no patient with multiple lesions had a haemorrhage in follow-up); the occurrence of a prior haemorrhage was the most important risk factor for re-haemorrhage. The authors did acknowledge, however, that their findings might be affected by selection bias, since their patients had been referred to a tertiary referral centre that specialized in microsurgical and radiosurgical procedures; nevertheless 61 patients in their study had never suffered a haemorrhage.

In Niigata University in Japan, Aiba and colleagues conducted a retrospective study, with 110 patients, 56% of whom presented with a haemorrhage (Aiba et al., 1995). They reported a first haemorrhage rate of 0.39% per patient-year in the seizure and incidental groups, where there was a single bleed in 254 patient-years of follow-up, and a re-haemorrhage rate of 22.9% per lesion per year in those who had initially presented with a symptomatic haemorrhage (45 haemorrhages in a mean follow-up period of 4.7 years), thus demonstrating the huge effect that prior haemorrhage has on the re-bleed rate. They also found that younger female patients (under 40 years of age) had a significantly higher risk of re-bleed compared to both male groups and female older age-groups, and they attributed this to female hormonal factors. They observed that recovery from initial haemorrhage was good, even when managed conservatively, unless the lesions occurred in eloquent areas of the brain; however, recurrent bleeds did result in permanent neurological deficits.

Porter and colleagues analysed the data of all the patients who had been referred to the University of Toronto Brain Vascular Malformation Study Group between 1989 and 1996. This is a prospective study with 173 patients at baseline (although follow-up was based on 110, because 63 were not considered to be eligible to be included in the study, as they could not contribute sufficient follow-up). Of the 173 adults, 25% presented with haemorrhage, 36% seizure, 20% FND and 12% incidentally. The mean follow-up ($n$ = 110) was 3.8 years, and an overall haemorrhage rate was calculated as 1.6% per patient-year (Porter et al., 1997). However, this rate includes adults who presented with ICH (two), FND (four) and incidentally (one), so it cannot be compared with other rates that are calculated as first or recurrent ICH.

They found that CCM location – not prior haemorrhage – was the most important, and statistically significant, risk factor for haemorrhage: in those with supratentorial lesions, there was a single haemorrhage (in a thalamic lesion) during 268 patient-years of follow-up (0.4% per year), compared with six haemorrhages in patients with infratentorial lesions during 160 patient-years of follow-up (3.8% per year) ($p$ = 0.008). If this was re-classified as deep versus superficial, then there were seven haemorrhages in 170 patient-years of follow-up (4.1% per year) of lesions in deep locations, compared with no bleeding in 258 patient-years of follow-up in superficial lesions ($p$ = 0.0003). When haemorrhage and FND (defined as 'clinical events') were examined by location, there was a single event among patients with supratentorial lesions (0.4% per year), whereas those with infratentorial lesions experienced 17 events, yielding an event rate of 10.6% per year ($p$ = 0.0001); all the events related to lesions in deep locations. Of the 59 patients who sustained an ICH or FND (either at presentation or during follow-up), 37% recovered completely, 36% had a partial recovery, but 27% showed no improvement at the end of follow-up. Interestingly, neither location, nor haemorrhagic versus non-haemorrhagic events affected the level of patient recovery (Porter et al., 1997).

Porter and co-workers contacted patients who had not been seen at the clinic in the twelve months prior to the end of the study by telephone, in an attempt to eliminate a potential follow-up bias. The researchers decided a priori that only ICH (or clinical events) where the patient had been examined would be included in the analysis, but

because no patient contacted by telephone had suffered an ICH (clinical event), this situation did not occur. This prompted their observation that patients who remain in good health are less likely to see their clinician and are more likely to become lost to follow-up. However, the authors make the interesting comment that had they not decided to contact these patients by telephone, these individuals would have been classified as lost to follow-up (Porter et al., 1997); if this situation had arisen, the prognosis would have appeared worse, since the data from several stable patients would have been missing and the denominator of patient-years of follow-up would have been smaller, thus resulting in an apparently greater haemorrhage risk.

In their retrospective study of patients who had attended the neurosurgical department at Clermont-Ferrand between January 1990 and March 2005, Ghannane and colleagues reported a haemorrhage rate of 6.3% per patient-year in the 39 patients who did not receive surgical intervention (Ghannane et al., 2007). In a study of all cranial MRI scans between mid-1990 and mid-1994 at Yonsei University College of Medicine in Seoul, Kim et al. reported recurrent haemorrhage rates of 3.8% per patient-year or 1.4% per lesion-year; they recommended surgical excision of lesions in patients with recurrent or acute progressive symptoms, and stressed the importance of complete removal of the lesion (Kim et al., 1997).

Fred Barker and colleagues at Massachusetts General Hospital, Boston, investigated whether haemorrhages from cavernous malformations had a tendency towards temporal clustering (Barker II et al., 2001). They retrospectively reviewed 136 patients who had presented with symptomatic haemorrhage and had subsequently been treated surgically or with proton-beam radiosurgery between 1978 and 1995; the total follow-up period, between first presentation and treatment, was 538 patient-years. During this time, 47 patients sustained a second haemorrhage and 16 had additional bleeds (12 had two re-bleeds, 2 three, and one person each had four and five re-bleeds), giving cumulative re-haemorrhage rates of 14%, 34%, 49%, 56% and 72% one, two, three, five or ten years after the initial haemorrhage. They discovered the monthly haemorrhage risk was 2% during the first 2.5 years, but that it declined spontaneously to less than 1% per month thereafter. They also noted that re-haemorrhage rates were higher in younger patients (up to 34 years), but that neither sex, lesion location, number

of previous haemorrhages nor time-interval between previous haemorrhages had any significant effect on re-haemorrhage rates.

Hasegawa and colleagues examined the long-term results for 82 patients with high-risk cavernous malformations who had been treated with stereotactic radiosurgery at the University of Pittsburgh between 1987 and 2000 (Hasegawa et al., 2002). At entry to the study, 76 (93%) had sustained multiple haemorrhages (range 2 to 7), and six had experienced a single haemorrhage but with a subsequent decline in neurological function; the lesions were located in critical brain areas (79% infratentorial location) and several patients had previously undergone surgery. The results were subdivided into two groups: pre-radiosurgery (time from first image-documented haemorrhage to radiosurgery, mean duration 4.3 years) and post-radiosurgery (mean duration 4.9 years). Average annual ICH rates were 33.9% and 12.3% respectively; however, when haemorrhage rate for each individual year in the pre- and post-radiology period is examined, the pre-treatment haemorrhage rate starts high, but gradually decreases by the sixth year, and the first-year post-treatment rate is similar to the sixth-year pre-treatment rate. The study design is somewhat questionable as the control group is the pre-radiosurgery group. Although the authors acknowledge Barker's research on temporal clustering, they argue that their series is different as fewer of Barker's patients (46%) experienced a second haemorrhage. The radiosurgical morbidity rate was 13.4%. The authors stress two points, however: first, the patients in this study were a highly select group, 93% of whom had sustained multiple haemorrhages and their lesions were located in areas of the brain that were associated with an unacceptably high surgical risk of morbidity, and second, that imaging technology is continually developing and hence the ability to target the lesion is improving. The authors suggested that younger patients who had sustained a single haemorrhage with major neurological deficit should possibly be considered for radiotherapy. However, several other clinicians have advised caution in interpreting these results (see the Comments, following the paper) and the need for further study (Kim et al., 1997, Porter et al., 1997).

*Familial cavernous malformations*

For 5.5 years, between mid-1986 and the end of 1991, Zabramski et al. studied cerebral cavernous malformations in six unrelated Arizona families, five of which were of Hispanic descent (Zabramski et al., 1994). Of 118 surviving family members, 59 were located and willing to participate in the screening evaluation; 31 patients (53%) were found to have at least one CCM on MRI, and of these, 21 people (15 symptomatic) agreed to take part in the prospective natural history study (mean follow-up 2.2 years). Three patients (two with epilepsy and one previously asymptomatic, who developed seizures during follow-up) had a re-bleed during follow-up, which resulted in a re-haemorrhage rate of 6.5% per patient-year or 1.1% per lesion-year. They discovered that the lesions changed in size and number (17 new lesions in six patients, giving a growth rate of 0.4 lesions per patient-year) during the comparatively short follow-up period, and recommended repeat imaging using gradient-refocused MRI at annual intervals for symptomatic patients.

Between December 1996 and October 1999, in a national French survey, Labauge et al. prospectively followed 33 clinically asymptomatic non-Hispanic patients with familial CCMs for a mean period of 2.1 years (Labauge et al., 2001). They confirmed the dynamic nature of this form of the disease and the appearance of 30 de novo lesions in ten patients during follow-up; they estimated a lesion growth rate as 0.4 lesions per patient-year. There were three haemorrhagic events: one clinically symptomatic (haemorrhage within the brainstem) and two asymptomatic: the symptomatic haemorrhage rate was 1.4% per patient-year (or 0.2% per lesion-year), and the total haemorrhage rate was 4.3% per patient-year (0.6% per lesion-year). They commented that the overall haemorrhage rate (calculated in lesion-years) in their study was similar to that of patients with the sporadic form of the disease; patients with the familial disease tend to have a higher incidence of haemorrhages because they tend to have multiple lesions, rather than one particular lesion tending to re-bleed more frequently.

*Brainstem cavernous malformations*

In a retrospective study, Fritschi and colleagues reviewed 139 cases of brainstem CCM and found a first haemorrhage rate of 2.7% per lesion per year (using the lifetime-risk method), and a re-haemorrhage rate of 21% per lesion per year; there was no difference between the sexes (Fritschi et al., 1994). They recommended that excision of symptomatic brainstem lesions should only be carried out by experienced surgeons in a few specialist centres, and that asymptomatic lesions should be monitored regularly; they also stated that the probability of a good surgical outcome in the case of deep lesions in the brainstem that lack a superficial extension was very small, due to their proximity to eloquent areas.

Randall Porter and colleagues retrospectively examined the case histories of 100 patients with brainstem CCMs who had attended the Barrow Neurosurgical Institute in Arizona between 1984 and 1997 (Porter et al., 1999); 97 had presented with a haemorrhage, and brainstem lesions were discovered in three people incidentally. All of the 86 patients whose lesions were surgically excised had an associated venous anomaly, which was preserved in tact in 85 cases to avoid the risk of venous infarction. The authors observed that the natural history of brainstem CCMs is worse than that of CCMs in other locations: the haemorrhage rate for brainstem CCMs is higher, and there is an increased probability of a re-haemorrhage (which in their series was 30.2% per patient-year). For this reason, they recommended surgical excision in cases where the symptomatic lesion abuts a pial surface or is surrounded by a thin rim of brainstem tissue. However, they also acknowledged that conservative management may be appropriate for people with an asymptomatic brainstem lesion or for people who have made a complete recovery from a single haemorrhage.

Mathiesen et al. prospectively followed 68 patients with brainstem or deep CCM who had presented at the Department of Neurosurgery at Karolinska Hospital in Stockholm between 1992 and 2000 (Mathiesen et al., 2003); 29 underwent microsurgery, five gamma knife surgery and 34 did not receive surgical intervention. The last group consisted of those with incidental lesions (11), those medically unfit, or with lesions where the risk of surgery was deemed unacceptably high. Through data linkage, the

authors calculated an incidence of 3.2 persons per million per year for those with symptomatic deep or brainstem CCMs, and 0.8 persons per million per year for incidental deep or brainstem CCMs in the catchment area for their institution, although they acknowledge that the latter figure is an underestimate of the true incidence of asymptomatic deep or brainstem CCMs. Analysing their data relating to the conservatively managed group, they concluded that incidental lesions had a low risk of neurological deterioration: an ICH rate of 2% per year compared with 7% per year in patients with symptomatic lesions. Thus they advocated that incidental brainstem or deep lesions should be managed conservatively, as did Wang and colleagues in Beijing (Wang et al., 2003). In a small study comparing six adults with brainstem lesions whose lesion was excised and 15 with brainstem lesions who were conservatively managed, Tarnaris and colleagues recommended that the 'conservative approach should not be so easily overlooked' (Tarnaris et al., 2008).

Mathiesen's group also stressed that timing of surgery appeared to influence the outcome and advised that patients should receive surgery between two and four weeks after ictus, but only if the surgeon was confident that total removal of the lesion was possible: partial removal resulted in a worse outcome than following conservative approach. Radiosurgery was not deemed to be an effective therapy for deep and brainstem lesions (Mathiesen et al., 2003, Wang et al., 2003, Hauck et al., 2009).

Two papers have been published more recently, examining the management of brainstem CCM. In the first paper, Erik Hauck and colleagues retrospectively reviewed clinical data of all patients who had presented with a symptomatic brainstem CCM at the Department of Neurosurgery at the University of Texas, Southwestern Medical Center, between 1995 and 2007, and who had subsequently had their lesion surgically excised ($n = 44$) (Hauck et al., 2009). In the pre-treatment period, twenty people had a single haemorrhage and 23 at least one recurrence; the median time between first and second events was two years, with the risk of a recurrence being 42% per year; eight patients had more than two events, and the median time between the second and third event was only five months, with a risk of a second recurrent event being 8.6% per month. Although women and younger patients (under 40 years) had a shorter event-free interval, sex and age were not statistically significant.

The risk of future recurrent events was reduced after surgery, but a comparison of pre- and post-operative scores on the modified Rankin scale did not demonstrate a huge improvement in patient outcome: only 30% had an improved outcome after surgery, whereas 70% remained the same (59%) or had a worse outcome (11%). In addition, there were a large number of surgical complications, and eight patients required repeat surgery. Weighing up both the increased risk of a haemorrhage after each successive event, and the fact that a patient's pre-operative condition is a strong predictor of their functional outcome after surgery, with the risks of surgery, the authors 'encourage neurosurgeons to consider surgery after a first event'. However, in his review of the paper, Christopher Ogilvy drew attention to the selection bias in the report: Hauck et al. only analysed patients with symptomatic brainstem lesions who had undergone surgery, which was a very distinct subgroup and was not representative of the population with brainstem lesions who had presented at the hospital. Ogilvy emphasized the surgical complication rate, and the fact that 70% of the sample did not experience an improved outcome (Hauck et al., 2009).

In the second paper, Abla and colleagues at the Barrow Neurological Institute in Phoenix, Arizona, retrospectively reviewed all the adult surgical cases of brainstem CCMs that Robert Spetzler, the senior author, had treated between 1985 and 2009 (Abla et al., 2011). (Some of these participants were included in the earlier paper by Randall Porter and colleagues (Porter et al., 1999).) Of the 260 adults (female : male ratio of 3 : 2), 252 (97%) had presented with either a clinical or radiographic history of haemorrhage, seven were suffering from progressive neurological deficits, and one lesion was discovered incidentally. Between presentation and surgery (mean time 4.5 years for those with multiple bleeds), 146 of the 252 patients experienced at least one re-bleed: 96 had one re-bleed, 32 had two, and 18 had three or more re-bleeds, leading to an annual re-bleed rate during the observation period of 35% per patient-year in these patients. The authors stressed that this re-haemorrhage rate was not typical of all patients with brainstem CCMs, as these patients had been referred to a tertiary specialist centre; the annual risk of haemorrhage for patients referred to the unit after a single haemorrhage was in the region of 15% per patient-year. After surgery, 18 patients (6.9%) sustained 20 haemorrhages, and 12 of these patients required a second operation; the annual risk of post-operative haemorrhage was calculated at 2% per

patient. In addition, 93 patients (36%) had permanent new neurological deficits. Eight deaths occurred between surgery and last follow-up; however, these deaths occurred in the first 88 patients, and the surgical technique changed during the course of the 24 years. The mean Glasgow Outcome Scale at admission, discharge and at last follow-up was 4.4, 4.2 and 4.6 respectively.

The authors concluded that in their institute surgery was offered to patients with symptomatic brainstem lesions that were surgically accessible, because of their increased risk of re-haemorrhage. However, if the symptoms are mild and the lesion deep-seated, then patients are observed to see whether a future bleed occurs and whether the lesion reaches a pial surface.

In his Comment on the paper, Robert Solomon drew attention to the referral and selection bias of the study, and the fact that the neurosurgeon was exceptionally experienced and his results might not be replicated by a less experienced neurosurgeon. In Solomon's experience the majority of patients with symptomatic brainstem cavernous malformations do not experience a second event, or, if they do, often have mild symptoms. Thus he did not agree with the authors' conclusion that surgery should be offered to any patient with a surgically-accessible and symptomatic brainstem CCM. Solomon recommended that most patients should be conservatively managed and surgery should only be offered to those patients experiencing multiple haemorrhages and progressive neurological decline (Abla et al., 2011, Haque et al., 2008). These differing views illustrate the fact that more research is needed, especially on the untreated clinical course of the condition, so that the risks of surgery can be weighed against the likely prognosis if conservative management is followed.

### *Cavernous malformations with associated venous malformations*

Abdulrauf and colleagues at Yale University School of Medicine retrospectively compared 55 consecutive patients, who had presented over the course of four years, with CCMs with and without associated venous malformations (venous developmental anomalies) ($n$ = 13 and 42, respectively). They observed that women are more

likely to have a CCM with an associated venous malformation (Abdulrauf et al., 1999), and these lesions (CCM + VM) were found more frequently in patients with the sporadic form of the disease. Patients with mixed vascular malformations tend to have lesions located in the posterior fossa; they are less likely to present with seizures, but more likely to present with symptomatic haemorrhage, and the disease will probably have a more aggressive course.

*Haemorrhage risk*

Point estimates of haemorrhage risk have been calculated in several of the published accounts (see Table 3.3), and are shown in 3.2. As can be observed, there is considerable variation in the risks for a recurrent haemorrhage; however, some of the variation is a result of the method used to calculate the risk rather than disparity in the actual risk of haemorrhage. Some researchers have included all haemorrhages after the initial one as a numerator, which obviously will inflate the risk of haemorrhage. A more useful method for patients is to include only second bleeds, to give a risk of a first recurrence, and to exclude third and subsequent events.

In a comment at the end of Moriarity and colleagues' paper, Issam Awad puts forward the proposition that the neuro-imaging policy of a hospital may influence the haemorrhage rates of CCMs in infratentorial and supratentorial locations in that establishment, and even whether the rates differ between the two CCM locations (Moriarity et al., 1999). Awad suggests that in some centres lesions are only scanned during follow-up if the patient experiences certain symptoms; in this scenario, more serious symptoms are more likely to be associated with lesions in infratentorial locations than those in supratentorial locations; therefore more patients with infra-tentorial lesions will be scanned and there is a greater chance of a symptomatic haemorrhage being detected in these locations. Conversely, there is a reduced chance of an asymptomatic haemorrhage being detected in supratentorial lesions, and this will affect the haemorrhage rate in this location. In centres where neuro-imaging is more frequent and the neuro-imaging threshold is lower, patients with lesions in either location will be scanned and more asymptomatic ICH will be detected: thus the

disparity between ICH rates in infratentorial and supratentorial locations may be less likely to exist in these centres. Awad argues that there does not appear to be a biological reason for the increased frequency of haemorrhage in infratentorial or deep lesions. Nevertheless, Porter and co-workers make a valid point when they assert that neurological deficit is of greater relevance to the patient, whether or not it is accompanied by radiological evidence of haemorrhage (Porter et al., 1997).

## 3.4 Summary

From the studies cited above, it can be observed that the course of the disease seems to be relatively benign for most people diagnosed with CCM, especially for those whose lesion is located in a supratentorial region. However, this research is limited to the risk of intracranial haemorrhage or focal neurological deficit in follow-up; for a small number of people with intractable epilepsy, the disease may appear to be less benign. In addition, patients with lesions located in the brainstem tend to have an increased risk of developing clinical symptoms and disability, because of the high density of eloquent tissue in that location (Berg and Vay, 2011).

The probability of a fatal haemorrhage is low for adults diagnosed with CCM, whereas the probability of complete or good recovery following an initial haemorrhage is high; indeed 80% of patients experience only a transient deficit after an initial bleed (Kuker and Forsting, 2008). Nonetheless, several researchers have noted an increased risk of re-bleeding after an initial haemorrhage, and with each subsequent haemorrhage there is a greater probability that the patient's outcome will deteriorate permanently; usually patients who sustain more than two haemorrhages from the same lesion suffer a persistent neurological deficit. Moreover the prognosis for brainstem lesions is worse, with a re-bleed rate greater than 5% per patient-year (Kuker and Forsting, 2008, Josephson and Al-Shahi Salman, 2011).

In their review, Maraire and Awad commented that most cerebral cavernous malformations are diagnosed between the ages of 20 and 50 years: patients who

present before they reach the age of 30 are more likely to be male, whereas women tend to present between the ages of 30 and 60 (Maraire and Awad, 1995). Patients who are younger than 40 years at presentation tend to suffer seizures, whereas focal neurological deficits and haemorrhage are more common in older patients and children (Requena et al., 1991, Maraire and Awad, 1995, Ebrahimi et al., 2009). However, El-Koussy and colleagues report no such sex-related modes of presentation in their large retrospective study of patients who were seen at Inselspital, a tertiary care centre and part of the University of Bern, in Switzerland, over the course of twenty years ($n$ = 347) (El-Koussy et al., 2011). Patients with lesions in infratentorial locations are more likely to present with FND, whereas those with supratentorial lesions are more likely to present with seizure (Robinson et al., 1991, Moriarity et al., 1999, Batra et al., 2009).

There is a certain level of disagreement among authors regarding risk predictors for haemorrhage. Robinson, Aiba, Abdulrauf, Moriarity and Wang all agree that women are more likely to experience a re-bleed than men, and Aiba also reports that younger women (under 35 years) have an increased risk of haemorrhage (Robinson et al., 1991, Aiba et al., 1995, Abdulrauf et al., 1999, Moriarity et al., 1999, Wang et al., 2003). On the other hand, Fritschi, Kondziolka, Porter, and Kuker and Forsting specifically state that there is no sex difference (Fritschi et al., 1994, Kondziolka et al., 1995, Porter et al., 1997, Kuker and Forsting, 2008), and Engelmann et al. write: 'based on more recent evidence, it is now generally accepted that CMs behave similarly in both genders' (Engelmann et al., 2011). Interestingly, data from the first Scottish cohort very definitely opposed this view; however, data from the second cohort are consistent with it (see Chapters 4 and 8 below).

Several researchers, including Aiba, Kupersmith and Zabramski, state that younger patients (under 35 years) have an increased risk of experiencing bleeds or re-bleeds (Zabramski et al., 1994, Aiba et al., 1995, Kupersmith et al., 2001). Robinson and colleagues, however, could find no evidence in their study that haemorrhage rates differed between younger and older patients (Robinson et al., 1991).

Prior haemorrhage was observed as a risk factor by Aiba and Kondziolka, although Moriarity categorically stated that it was not a risk factor in his study (Aiba et al., 1995, Kondziolka et al., 1995, Moriarity et al., 1999). Phillip Porter and colleagues found

that most people who experience haemorrhage or a focal neurological deficit in follow-up had already experienced a prior haemorrhage or FND, but they did not find an association with sex; they explicitly stated that 'lesion location, and not previous haemorrhage, is the most important factor in predicting haemorrhage or events' (Porter et al., 1997). They observed 18 haemorrhages and FNDs during follow-up in patients with deep lesions (17 infratentorial and one thalamic), and no events in patients with superficial lesions. Moriarity and co-workers reported that patients with infratentorial lesions were significantly more likely to present with FND than patients with a supratentorial lesion ($p = 0.003$) (Moriarity et al., 1999). In their study on temporal clustering, Barker et al. suggested that the risk of a lesion re-bleeding was elevated for 2.5 years immediately following the bleed, then it reverted spontaneously to a lower level (Barker II et al., 2001). In his Comment at the end of Moriarity's paper, Issam Awad suggests that some of the discrepancy among researchers regarding re-haemorrhage rate may be due to the fact that surgeons in different medical establishments operate at different stages in the clinical course. Some will decide to excise a lesion soon after the initial haemorrhage, thereby providing a very short window for a re-haemorrhage to occur and hence a potentially lower risk of re-haemorrhage at that institution, whereas others will be more cautious and allow a longer time to elapse, during which the individual may re-bleed (Awad in (Moriarity et al., 1999)).

No researchers observed a statistically significant association between lesion size and risk of haemorrhage (although Kupersmith and co-workers commented that lesions that were larger than 1 cm in diameter were associated with a higher risk of bleeding) (Kupersmith et al., 2001). Neither CCM multiplicity, nor the form of the disease (sporadic versus familial), nor seizure at presentation were associated with an increased risk of haemorrhage.

Several authors stated in their conclusions that a larger, prospective study with a longer follow-up period was required (Del Curling et al., 1991, Fritschi et al., 1994, Maraire and Awad, 1995, Yoon et al., 1998, Abdulrauf et al., 1999, Hauck et al., 2009). In 1999, a prospective, population-based study began recruitment – the Scottish

Intracranial Vascular Malformation Study (SIVMS) (http://www.saivms.scot.nhs.uk/) (Al-Shahi et al., 2003a) – in order to address this vacuum in the research.

## 3.5 Addendum

This chapter is based on the literature search and review that I included in my first-year report (November 2011). In September 2014, I updated the two database searches to check for publications in the intervening period (2010–current). I found 185 records in the Embase search and 122 in the Medline search. The combined searches contained 27 duplicate records, and a further 229 records that were not relevant (genetic studies, case reports or less than 20 sample size, imaging reports, or children, or too specialized) were deleted. Of the 51 remaining records, eleven examined the untreated clinical course (including our paper and two from our collaborators at the Mayo Clinic) and four functional outcome (two of which were abstracts in conference proceedings). However, I discovered no new information about the risk of haemorrhage in untreated follow-up. I had previously read four of the eleven papers and a fifth was a reprint of a paper published in the 1990s; two Chinese papers were restricted to brainstem lesions, and were an update of an earlier paper (Wang et al., 2003); and a small series of 29 surgical patients were described in a Brazilian paper (De Araujo Jr et al., 2011).

With the benefit of hindsight, were I to embark on a review of the literature again, I would create more tables in greater detail, before starting the reading, to facilitate a more systematic means of note-taking. However, I would stress that my intention was to provide a concise review of the literature available at the time, rather than to undertake a full-blown systematic review.

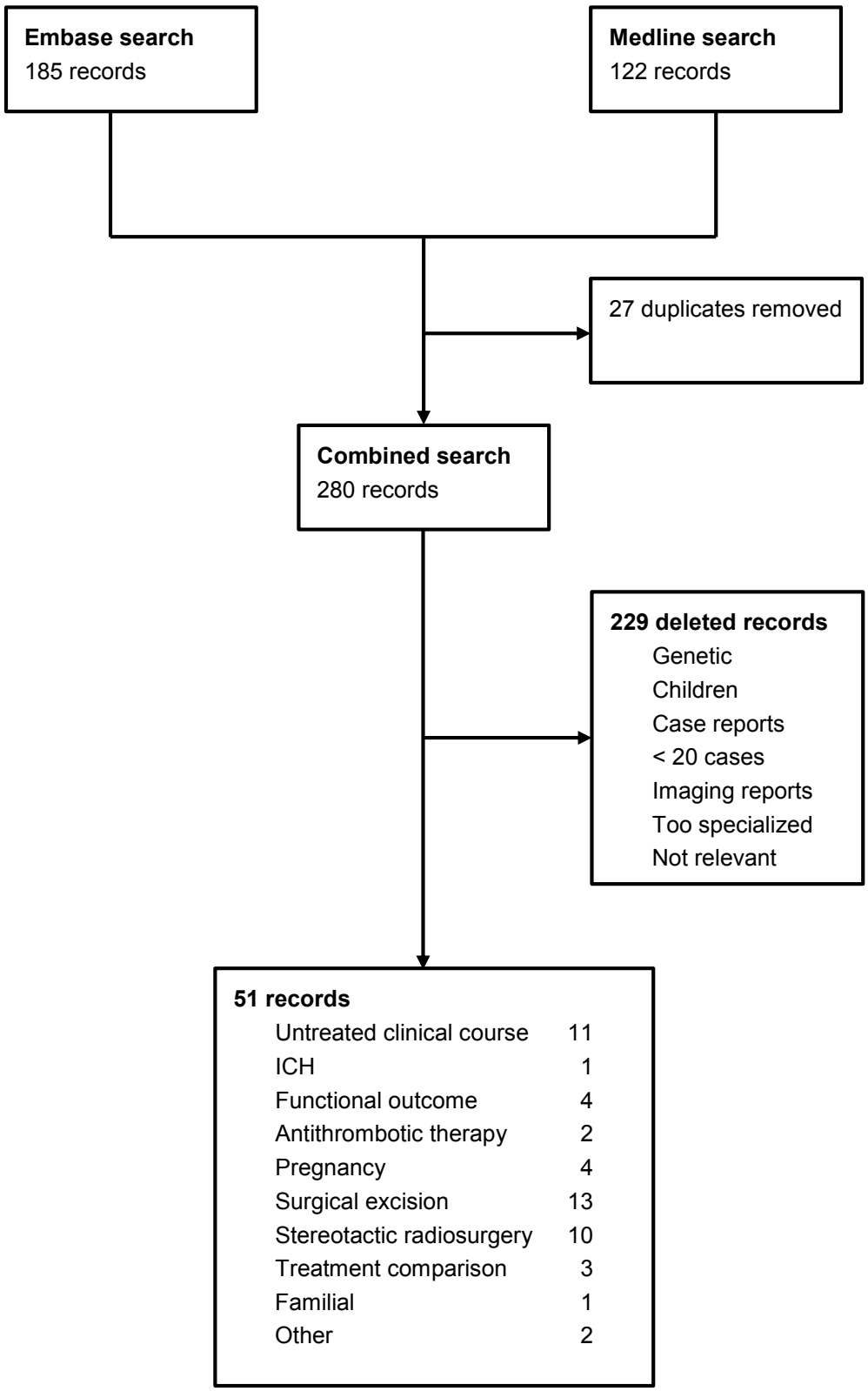



**Figure 3.3 Flowchart of updated literature search**

# Chapter 4: Estimated risk of intracranial haemorrhage or focal neurological deficit in untreated follow-up in the two Scottish cohorts

## 4.1 Background

Until the end of the 1990s, apart from a small prospective population-based study in Olmsted County, Minnesota (Brown et al., 1996), all cavernous malformation data were derived from hospital-based and often retrospective studies, and were often based on post-mortem examination. As discussed in Chapter 3 above, this introduced many forms of bias, including selection bias and case-ascertainment bias, since people with asymptomatic CCMs or mild cases would not have been seen in hospital, and only those with more severe symptoms would probably have been referred to a tertiary neurological centre, where most research groups are based. Thus prospective, population-based studies of people with cerebral cavernous malformations were needed so that the prevalence of the condition in a stable population could be estimated, and its clinical course and various treatments could be studied (van Beijnum et al., 2008).

It is important to note that in this thesis the description 'prospective population-based study' has a more restrictive meaning than in common epidemiological usage. For example, the Scottish Intracranial Vascular Malformation Study is frequently described as a prospective population-based study, because it recruits all adults resident in Scotland (i.e. population-based, rather than patients from a particular hospital or group of hospitals) who have received a first-in-a-lifetime intracranial vascular malformation diagnosis that has been validated by brain MRI or pathological

examination within two five-year time-periods. The date of presentation or date of diagnosis is set as the study inception, and all follow-up from this point onwards is prospective. It should be borne in mind, however, that the population from which the cohort is recruited must have either had a brain MRI or undergone brain surgery, in addition to being resident in Scotland during the study recruitment period.

There are other people in Scotland who have some form of intracranial vascular malformation (of which CCM is one type) that is quiescent, who have never needed to have a brain MRI for any other cause, and who are therefore unaware of their underlying condition; although these individuals are asymptomatic and have the disease, their condition has not – yet – been diagnosed (and indeed may never be diagnosed). Brain MRI, however, is increasingly being used as an investigative tool for people who have suffered a traumatic brain injury, migraine sufferers, people with other symptoms or underlying medical conditions, and healthy research volunteers. It is estimated that about 1 person in 625 who have a brain MRI will receive an incidental CCM diagnosis, even though they have not experienced any symptoms related to the disease. Therefore it is crucial that more research is conducted on the risk of future ICH or FND for people with CCM who present incidentally, so that clinicians and future patients can make decisions on a management plan after incidental CCM diagnosis, informed by the likely course of the untreated cavernous malformation.

Although randomized controlled trials (RCTs) are the optimum means of assessing treatment effects, prospective population-based studies nevertheless play a part in generating effect estimates and planning RCTs. Longitudinal observational cohort studies benefit from a long follow-up period; for example, in the case of SIVMS, everyone in the earlier cohort has a minimum of eleven years of follow-up to date. To answer accurately the question of how the untreated clinical course of the disease progresses, a minimum length of follow-up of at least two decades is likely to be required, and ideally follow-up will continue for the duration of the cohort members' lifetime. Longitudinal cohort studies are also useful for comparing long-term patient outcome after interventional treatment and conservative management.

## 4.2 Methods

### 4.2.1 Study questions

In this chapter, clinical and functional outcomes of Scottish residents who were diagnosed with cerebral cavernous malformation between 1999 and 2010 are investigated. The following questions are addressed.

1. What are the estimated five-year risks of first and second intracranial haemorrhages definitely due to CCM?
2. What are the estimated five-year risks of first and second clinical events (intracranial haemorrhage or focal neurological deficit), definitely or possibly due to CCM?
3. Which baseline characteristics modify the risk of ICH or FND occurring within five years of CCM diagnosis?
4. Over the course of five years, from the time of the first clinical event, how does the level of dependency compare for adults who have had a single clinical event and for those who have had a recurrence?

### 4.2.2 Scottish Audit of Intracranial Vascular Malformations

Since Scotland is a geographically distinct area, with its own health service and a fairly stable population of 5.06 million in 2001 (annual influx was 0.3% between 2000 and 2001), which was large enough to support a register of cavernous malformations, it seemed an ideal location in which to set up a prospective population-based study. Thus the Scottish Intracranial Vascular Malformation Study (SIVMS) was established in 1998 to enable researchers to investigate the clinical course of the most common intracranial vascular malformations. SIVMS is the research arm of the Scottish Audit of Intracranial Vascular Malformations (SAIVMs, http://www.saivms.scot.nhs.uk/ ), which is a National Health Service clinical audit of all adults living in Scotland at the

time of receiving a first-ever diagnosis of any type of intracranial vascular malformation (IVM) during two five-year periods: 1999–2003 and 2006–2010 (Al-Shahi et al., 2003a, Cordonnier et al., 2008).

Multiple overlapping sources of case ascertainment were used to identify all adults diagnosed with an intracranial vascular malformation in Scotland within these two time-periods. The major source was a collaborative nationwide neuroscience network of physicians, surgeons, radiologists and pathologists who were affiliated with the clinical neurosciences and neuro-imaging facilities in Scotland. Clinicians in similar specialties who worked in hospitals in Newcastle and Carlisle were also approached, to ensure that any patients living close to the Scottish/English border who attended English hospitals were not missed. In addition, the Information Services Division (ISD) provided hospital discharge and death certificates relating to patients with an *ICD-10* (*International Classification of Diseases, 10$^{th}$ revision*) code for an IVM, and in the first year all 3,700 general practitioners (GPs) in Scotland were contacted to ascertain whether they had any patients who were not already known to SIVMS. No new adults were recruited from the GP survey, so this was not repeated (Al-Shahi et al., 2003b, Al-Shahi Salman, 2005).

Although recruitment to SAIVMs ended on 31 December 2010, all participants in the audit are followed up annually, for an indefinite length of time, using multiple overlapping sources. On the anniversary of IVM diagnosis, each participant's GP is contacted to report their patient's functional outcome on the Oxford Handicap Scale (OHS) (Bamford and Sandercock, 1989). In addition, GP medical notes and hospital notes are reviewed in an annual surveillance, and some participants agree to complete annual questionnaires on their functional outcome (based on the Barthel Index, Short-Form 36, and Hospital Anxiety and Depression Scale), with additional questions relating to the occurrence of nose bleeds, epilepsy, stroke and whether the participant has been hospitalized since the previous preview.

### 4.2.3 Study design

As described above, SIVMS is a prospective, population-based observational cohort study that aims to include all adults who were permanently resident in Scotland at the time of a first-in-a-lifetime definite diagnosis of any of the three major intracranial vascular malformations: brain arteriovenous malformation, dural arteriovenous fistula and cerebral cavernous malformations. All participants included in this analysis were aged 16 years or over when they received a first-ever CCM diagnosis that had been validated by brain imaging (MRI) or pathological examination.

### 4.2.4 Procedures

For this analysis, inception is taken as the date of a participant's initial presentation that resulted in a medical investigation and a subsequent CCM diagnosis. For patients whose CCM was asymptomatic, inception was taken as the date of the medical consultation that led to the clinical investigation as a result of which a CCM was diagnosed.

The follow-up period was five years after inception. The period of time between the date of presentation and the date of diagnosis is considered to be retrospective, and time from date of diagnosis onwards is prospective. Although more follow-up was available for the earlier cohort and also for some adults in the second cohort, a decision was taken to truncate follow-up at five years to encourage the standardization of outcomes and follow-up length, in order to facilitate comparison with other studies. This topic is discussed in greater depth in Chapter 6 (subsection 6.6.2) below.

In cases where the patient presented with several symptoms, the dominant type of clinical event was reported as the presenting event: for example, in the case of someone who presented with a headache, an epileptic seizure and an intracranial haemorrhage, the haemorrhage would be recorded as the type of presentation, since the other conditions are symptomatic of haemorrhage.

Distinctions were drawn between intracranial haemorrhage, non-haemorrhagic focal neurological deficit (where there is no evidence of recent blood on timely brain imaging or pathological examination) and focal neurological deficit not otherwise specified (where neither neuro-imaging of the appropriate modality nor pathological examination had been performed at all or at the correct time to be able to distinguish recent blood), according to published criteria (Al-Shahi Salman et al., 2008), for clinical events both at presentation and in follow-up. These outcome events were categorized as being either definitely due to the CCM or possibly due to the lesion (there being no other adequate explanation).

Initial presentation was categorized as 'incidental' if an adult was asymptomatic (for example, an MRI might have been performed after a traumatic head injury) or if their symptoms (e.g. headache, tinnitus or other neurological deficit) could not be ascribed to the underlying cavernoma. Initial presentation was classified as epileptic seizure if the seizure was neither symptomatic of a concomitant intracranial haemorrhage nor more likely to be due to another cause.

### 4.2.5 Data extraction

For this investigation, two anonymized datasets per cohort were extracted from the SAIVMs database: one outcome was first intracranial haemorrhage attributable to a cerebral cavernous malformation that occurred after presentation, and the second was intracranial haemorrhage or focal neurological deficit, attributable or possibly attributable to a cerebral cavernous malformation, that occurred after presentation. Each dataset was imported as a flat-form datasheet into SPSS via MS Excel.

At this stage, however, data were displayed so that each row represented a cavernous malformation, whereas the intention of the analysis was to create a model that would predict outcome for the patient, rather than according to the CCM. In addition, it would create statistical problems if the analyses were performed with individual lesions as the observational unit, rather than patients: in the former case, the assumption of independence of observations would no longer be valid, as the same patient

characteristics would be represented multiple times for those patients who had more than one cavernous malformation. Therefore the four datasheets needed to be de-duplicated so that each row represented a single adult.

When an adult harbouring multiple lesions presented symptomatically, with a seizure, haemorrhage or focal neurological deficit, the mode of clinical presentation was attributed to the symptomatic lesion, and the row relating to this lesion was used in this analysis; the rows pertaining to the other lesions were deleted, after inspection that no other information relating to the adult was included in them. On the other hand, when an adult with multiple lesions presented asymptomatically or their CCM diagnosis was incidental, then brainstem location took precedence as the primary CCM location, and the rows for the other lesions were deleted.

The basis for this decision to include brainstem lesions in the analysis in preference to lesions in other locations, in cases where a primary lesion could not be detected and at least one brainstem CCM was present, was the hypothesis that brainstem location was a predictor of intracranial haemorrhage or focal neurological deficit since lesions located in the brainstem are adjacent to eloquent areas of the brain and can thus do more damage than when they are situated in other parts of the brain. If this decision were to result in an over-classification of brainstem lesions among patients with multiple lesions, then it is possible that the association between brainstem location and ICH or FND in follow-up might be weakened. The number of patients (and lesions) affected by this classification compromise should be reported to ascertain the scale of the potential problem. In cases where adults harboured multiple lesions, but none were located in the brainstem and none had undergone interventional treatment, a random row was selected to represent that adult.

Data completeness for each cohort was quantified as total actual data obtained as a percentage of total potential data (Clark et al., 2002).

## Composition of the datasets

The composition of the datasets used for the analyses reported in this chapter is described in the following two subsections. In Table 4.1, datasets are labelled according to the cohort, the mode of clinical presentation (or whether an outcome event has previously occurred in follow-up, for those adults presenting incidentally or with a seizure), and the outcome event in the analysis. Reference will be made to this table and Figures 4.1–4.2, in the next two subsections, in an attempt to clarify the composition of each dataset and which research question they are addressing.

### *Time to first ICH attributable to CCM*

For each cohort, the first analysis investigated either the estimated risk of experiencing a first ICH attributable to a CCM within five years of presentation (or until the date of first intervention, if the management strategy included interventional treatment), for those who had presented with a seizure or incidentally (i.e. datasets A and E in Table 4.1), or the estimated risk of a recurrent ICH attributable to a CCM within five years of presentation (or until date of intervention), for those who had suffered a prior ICH due to a CCM, either at presentation or within five years of untreated follow-up (datasets C and G in Table 4.1). Figure 4.1 displays which adults are included in this outcome graphically.

Thus the dataset for each cohort was formed by merging datasheets for each of the following four groups:

(i) those who presented with a seizure or incidentally *(sets A and E)*;
(ii) those who presented with an ICH attributable to a CCM *(sets C and G)*;
(iii) those who presented with a seizure or incidentally, and suffered an ICH due to a CCM within five years of untreated follow-up *(included in sets C and G)*; and
(iv) those who presented with an FND, and suffered an ICH due to a CCM within five years of untreated follow-up *(included in sets C and G)*.

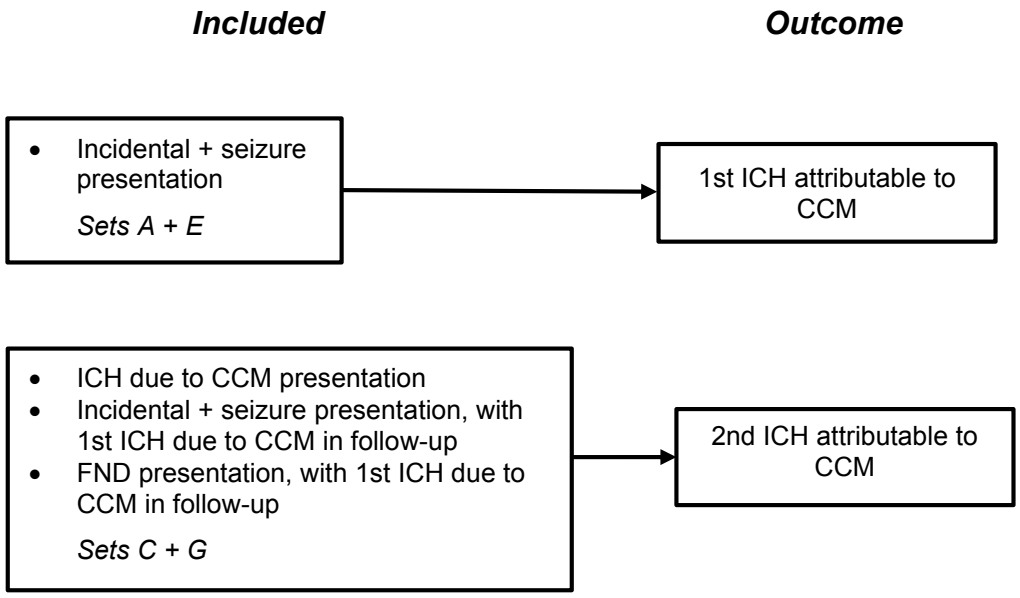



**Figure 4.1 Adults included and outcomes for first analysis, ICH attributable to CCM**

Those who presented with an FND, but did not experience an ICH attributable to a CCM within five years of untreated follow-up were not included in this analysis. This decision was taken because there was potential uncertainty whether the FND at presentation was actually an ICH, either without the correct neuro-imaging having been performed or because the CCM obscured the blood on the imaging. A small number of people were included in both outcomes – i.e. first and recurrent ICH: namely those who presented with an FND, seizure or incidentally, but suffered an ICH due to a CCM during a maximum of five years' untreated follow-up.

**Table 4.1 Composition of datasets used to answer research questions**

| Presentation: / Outcome: | Incidental + seizure presentation | | ICH presentation / in follow-up | ICH + FND presentation / in follow-up |
|---|---|---|---|---|
| Cohort | 1st ICH | 1st ICH + FND | Recurrent ICH | Recurrent ICH + FND |
| **Cohort 1** 1999–2003 | set A | set B | set C | set D |
| **Cohort 2** 2006–2010 | set E | set F | set G | set H |

*Time to first clinical event*

In this analysis the outcome was broadened to include haemorrhages that were possibly due to a CCM, in addition to focal neurological deficits, due or possibly due to CCM; these are subsequently referred to as 'clinical events' in this thesis.

There are several reasons for including focal neurological deficits in this analysis. First, the effect of a non-haemorrhagic FND can have a similar degree of severity on a patient's functional outcome as the effect of an ICH. Second, as discussed in Chapter 2 above (section 2.3.2), diagnosis of an ICH is dependent on the appropriate neuro-imaging modality being performed at an appropriate time: blood can only be detected using CT within a week of the bleed, after which MRI is required, and sometimes an ICH can be obscured on a scan by the CCM and haemosiderin ring. Third, if patients and their clinicians have agreed on a strategy of conservative management, patients may be reluctant to report minor symptoms that may actually indicate a small symptomatic haemorrhage to their doctors, and similarly doctors may decide not to proceed to investigate minor or transient symptoms, when a cavernous malformation has previously been diagnosed (Josephson and Al-Shahi Salman, 2011). Thus it is apparent that the distinctions between the classification of a haemorrhage and a focal neurological deficit can on occasion be rather blurred, and symptoms that have been diagnosed as FND might in reality be small ICH.

In this analysis, the estimated risk of suffering a first ICH or FND due or possibly due to CCM for those adults who presented with a seizure or incidentally (i.e. sets B and F of Table 4.1) was compared with the estimated risk of suffering a recurrent ICH or FND for those who had suffered a prior clinical event, either at presentation or within five years of untreated follow-up (sets D and H of Table 4.1). The two groups are displayed graphically in Figure 4.2.

The dataset for each cohort was again formed by merging datasheets for each of the following three groups:

(i) those who presented with a seizure or incidentally *(sets B and F in Table 4.1)*;

(ii) those who presented with an ICH or FND attributable or possibly attributable to a CCM *(sets D and H)*; and

(iii) those who presented with a seizure or incidentally, and suffered a clinical event due or possibly due to a CCM within five years of untreated follow-up *(included in sets D and H)*.

Again, a small number of people were included in both outcomes – i.e. first and recurrent clinical events: those who presented with a seizure or incidentally, but suffered a clinical event due or possibly due to a CCM during a maximum of five years' untreated follow-up.

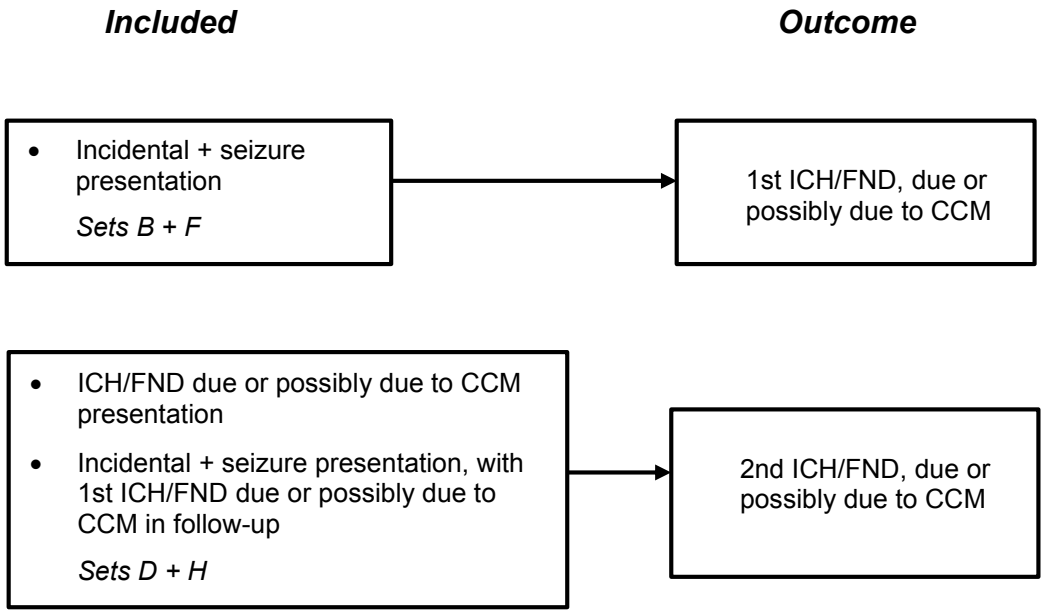



**Figure 4.2 Adults included and outcomes for the analysis of clinical event attributable or possibly attributable to CCM**

### 4.2.6 Statistical analysis

#### Descriptive analysis

First, tables of baseline characteristics, stratified by mode of clinical presentation, were created for the individual cohorts and both cohorts combined. The tables for the two individual cohorts were compared to ascertain whether any changes had occurred over the course of the twelve-year recruitment period.

At baseline, CCM location was categorized into four groups: brainstem (in the midbrain, pons or medulla), cerebellar, deep (in the thalamus, basal ganglia or choroid), or lobar (in the cortex or subcortical areas of the cerebral hemispheres). However, in the survival analyses, CCM location was dichotomized into brainstem CCM versus other location.

#### Time-to-event analysis

Throughout this thesis, time-to-event data, rather than continuous data, are analysed, since what is of interest is the length of time that elapses between the start of follow-up and the occurrence of a specific outcome (for example, ICH) over a period of time. For the data in Chapters 4 and 5, the start of follow-up is the date of first presentation that leads to a first-ever CCM diagnosis. Not all adults in the study will experience the endpoint of interest (i.e. ICH), but they may nevertheless be known to have survived for a certain period of time event-free; in this study, for example, they may have undergone interventional treatment, become lost to follow-up (withdrawn from the study), or have died, or have reached the end of follow-up (five years from presentation date, in this analysis), without having suffered a haemorrhage. In all these scenarios, the individual is considered to have been (right) censored at the earliest occurrence of treatment, withdrawal or death, and although these censored adults have not experienced the outcome of interest, they are still able to contribute valuable data until the time of censoring.

*Survivor function and hazard function*

The two main functions used to describe time-to-event data are the survivor function and the hazard function (Collett, 2003). The survivor function, *S(t)* is defined as the probability that an individual survives from the start of follow-up to at least as long as time *t*:

$$S(t) = P(T \geq t) = 1 - \int_{u=0}^{t} f(u)du$$

where *f(u)* is the underlying probability density function of *T,* and is defined as:

$$f(u) = \lim_{\Delta\tau \to 0} \left( \frac{\mathrm{P[death\ in\ interval\ (\tau, \tau+\Delta\tau)]}}{\Delta\tau} \right),$$

and $\Delta\tau$ is a very small time interval (Machin et al., 2006).

The hazard function, *h(t),* represents the instantaneous rate of dying at time *t*, conditional on an individual surviving up to time *t*, and is defined thus:

$$h(t) = \lim_{\Delta\tau \to 0} \left( \frac{\mathrm{P}[\tau < t < \tau + \Delta\tau | \tau < t]}{\Delta\tau} \right).$$

The survivor function, hazard function and probability density function can be expressed in terms of each other:

$$f(t) = \frac{d}{dt}[1 - S(t)]$$

$$h(t) = \frac{f(t)}{S(t)} = -\frac{d}{dt}[\log S(t)]$$

Integrating the last equation results in:

$$\int_{u=0}^{t} h(u)du = H(t) = -\log S(t)$$

or

$$S(t) = \exp[-H(t)].$$

$H(t)$ is the cumulative hazard. The survivor function and hazard function are estimated from the observed survival data.

*Kaplan-Meier estimate of the survivor function*

There are two main non-parametric methods used for analysing time-to-event data: the actuarial, life-table method and the Kaplan-Meier method (Collett, 2003). The former is well-suited when the actual times of the event are unknown, which is not the case in this thesis; therefore the Kaplan-Meier method is used throughout the three analyses, and is briefly described below.

The basic concept underlying the Kaplan-Meier estimated survival method is that the probability of surviving for a complete year is the probability of surviving for the 365$^{th}$ day, given that an individual has already survived 364 days (Machin et al., 2006). This can be written as:

$$S(365) = p_1 \times p_2 \times \ldots \times p_{364} \times p_{365}$$

where $p_1$ is the probability of surviving at least one day after presentation,
$p_2$ is the conditional probability of surviving a second day, having already survived the first day,
and $p_3$ is the conditional probability of surviving a third day, having already survived the second day, etc.

The probability of survival to time *t* is thus:

$$S(t) = p_1 \times p_2 \times \ldots \times p_{t-1} \times p_t.$$

For any time *t,*

$$p_t = \frac{Number\ of\ patients\ followed\ for\ at\ least\ (t-1)\ days\ and\ who\ survive\ day\ t}{Number\ of\ patients\ alive\ at\ end\ of\ day\ (t-1)}$$

If there are $n$ individuals in the study, with survival times $t_1$, $t_2$, $t_3$,…, $t_n$, and there are $r$ deaths, since probably not all $n$ people will die, and some may die on the same day (so $r \leq n$), then the death times can be ordered such that $t_1 < t_2 < t_3 <\ldots< t_r$ (Collett, 2003, Machin et al., 2006). At time $(t_i - \delta)$, an infinitesimal interval before time $t_i$, there are $n_i$ individuals alive (including those who are just about to die) and $d_i$ die at time $t_i$. The probability of a death occurring between time $(t_i - \delta)$ and time $t_i$ is $d_i / n_i$, and therefore the probability of survival during that period is:

$$1 - \frac{d_i}{n_i} = \frac{n_i - d_i}{n_i}$$

When an individual is censored at exactly the same time as a death occurs, the death is considered to take place first. When there are no deaths, i.e. between time $t_i$ and time $(t_{i+1} - \delta)$, the probability of survival is 1. Under the assumption that each death is independent, the Kaplan-Meier (or product-limit) estimate of the survivor function for the period between time $t_k$ and time $(t_{k+1} - \delta)$, and all the earlier intervals, is

$$S(t) = \prod_{i=1}^{k} \left(\frac{n_i - d_i}{n_i}\right).$$

The estimates of $S(t)$ can be drawn in a Kaplan-Meier plot, which is a distinctive step function, as the estimated survival probabilities remain constant between adjacent deaths, and then decrease at the time of each death.

### *Comparison of two survival curves*

The Kaplan-Meier plot is very useful when comparing the survival curves of two (or more) groups of individuals, for example, examining whether progression to five years of presentation is similar for men and women. The log-rank test is a non-parametric hypothesis test that is used to ascertain whether there is a difference between the two survival curves, and the basic premise underlying this test is that, if the two survival distributions actually are identical, then deaths (the outcome events) should be distributed between the two groups in proportion to the number of individuals at risk, (Collett, 2003, Machin et al., 2006). The log-rank test has the advantage that it uses all

the data for the entire duration of follow-up, rather than comparing the two curves at a single point in time. On each day (or whatever time unit is used) that a death (event) occurs, for each group the number of individuals at risk and the number of deaths (events) on that day are calculated; these are the observed values. As for the standard $\chi^2$ test, the number of expected deaths is calculated for each group, and the difference between observed and expected values are calculated for each group. There are several methods of calculating the log-rank statistic, but this is probably the easier to perform by hand:

$$\chi^2_{log-rank} = \frac{(O_A - E_A)^2}{E_A} + \frac{(O_B - E_B)^2}{E_B}$$

where $O_A$ and $O_B$ are the sums of the observed values for groups A and B on each day of death (event) respectively, and similarly $E_A$ and $E_B$ are the sums of the expected values for groups A and B on each day of death (event) (Machin et al., 2006). As a check, if performing this calculation by hand

$$O_A + O_B = E_A + E_B.$$

This log-rank statistic is then compared with the $\chi^2$ distribution with 1 degree of freedom (for a two-group comparison) to obtain the level of significance.

*SIVMS data*

For the analyses of recurrent ICH, follow-up started at presentation date for those who presented with an ICH or at date of first ICH in follow-up, for those with a non-haemorrhagic presentation. Similarly, in the analyses for recurrent clinical event definitely or possibly due to CCM, follow-up started at presentation for those who presented with ICH or FND, or at date of first clinical event for those who presented with a seizure or incidentally.

The focus of this analysis is the untreated clinical course of cerebral cavernous malformations, and the outcomes are either (i) first ICH definitely due to CCM or (ii) first ICH or FND, definitely or possibly due to CCM. Follow-up is censored at the earliest occurrence of first interventional treatment, in addition to death unrelated to

CCM, or last available follow-up. Therefore the length of follow-up for those who had an outcome event within five years of presentation was the time that elapsed between presentation and the event, and for those who did not have an outcome event, the length of follow-up was calculated as the time between presentation and censoring or the end of follow-up (which was truncated at five years).

Kaplan-Meier survival curves were used both to estimate the five-year risk of a clinical outcome (Kirkwood and Sterne, 2003, Machin et al., 2006), and together with log-rank tests, to test whether there was a difference between the two groups (i.e. those who presented incidentally or with a seizure and those who presented with a haemorrhagic presentation).

Given the size of these two cohorts, there were unlikely to be sufficient outcome events to build a prognostic model. However, Kaplan-Meier plots, stratified by (i) sex and (ii) CCM location, were produced to investigate in an exploratory analysis the effect of these two binary baseline characteristics on the progression to ICH or clinical event. These two variables were selected, in that order, as possible predictors of ICH or FND, on account of their clinical significance and existing evidence base (Robinson et al., 1991, Aiba et al., 1995, Kondziolka et al., 1995, Moriarity et al., 1999, Josephson and Al-Shahi Salman, 2011, Al-Shahi Salman et al., 2012, Flemming et al., 2012), in addition to their completeness, accuracy and reliability.

### Level of dependence after a first clinical event

As described in section 4.2.2 above, as part of the SIVMS follow-up, participants' general practitioners are contacted annually, at around the time of the anniversary of CCM diagnosis, to rate their patients' functional outcome using the Oxford Handicap Scale (Bamford and Sandercock, 1989). The Oxford Handicap Scale (OHS) is a six-point evaluation of the level of patient handicap, developed from the modified Rankin Scale (van Swieten et al., 1988); the OHS ranges from 0 (no handicap) to 5 (severe handicap: patient totally dependent and requires constant attention, day and night), although it is frequently informally extended to include grade 6, dead (see Table 5.1).

In this study, annual OHS ratings were examined for those patients who had experienced a first clinical event, either at presentation or during follow-up if they had presented with a seizure or incidentally. For the eight adults in the first cohort and the three in the second who presented with a seizure or incidentally, but suffered an ICH or FND within five years or presentation, their OHS ratings were adjusted so that the first rating they contributed to year one of follow-up was the first that was given after their first clinical event. If more than 18 months elapsed between the clinical event and the subsequent OHS score, then the score was included in the following year.

Patients were divided into two groups: those who experienced a second clinical event during five-year follow-up, and those who did not. Stacked bar charts for each group were created, showing the percentage of adults ranked on each OHS grade; the bar charts covered presentation and each of the five years of follow-up. As a sensitivity analysis, an additional stacked bar chart with the inclusion of those who had undergone interventional treatment was created for each cohort.

## 4.3 Results

### 4.3.1 Baseline characteristics

In the five years between 1999 and 2003, 141 adults who were aged 16 years or over and resident in Scotland were diagnosed with a definite first-time cerebral cavernous malformation that was validated by magnetic resonance imaging or pathological examination, and between 2006 and 2010, 166 adults received a similar definite first CCM diagnosis. Five adults in the earlier and one in the later time-period were diagnosed incidentally at autopsy, however, and these individuals were not included in the analysis. Therefore the earlier cohort consists of 136 adults, and the later one of 165 participants. The six adults who were diagnosed after death all presented incidentally; their baseline characteristics are displayed in Table 4.2. Data completeness for the first and second cohorts was 96.3% and 90.6% respectively.

**Table 4.2 Baseline characteristics of adults diagnosed at autopsy**

| Characteristic | 1999–2003 cohort | 2006–2010 cohort |
|---|---|---|
| Total | 5 | 1 |
| Sex | | |
| Male | 4 | 1 |
| Female | 1 | 0 |
| Age (median, IQR) | 78 (52–82) | 48 |
| Multiplicity | | |
| Single | 4 | 1 |
| Multiple | 1 | 0 |
| CCM location | | |
| Brainstem | 2 | 1 |
| Lobar | 3 | 0 |

Baseline characteristics of the two cohorts, stratified by mode of initial clinical presentation, are displayed in Tables 4.3 and 4.4 below. Over 40% of adults presented incidentally, and of those with symptomatic lesions, about half presented with a seizure, and the other half with either an ICH or FND. The percentage with FND presentation was 15% in 1999–2003, compared with 6% in 2006–2010; however, the median age for FND presentation among adults in the first cohort was substantially younger than that in the second cohort (40 versus 57 years).

Age at presentation increased slightly in the second cohort: median age in the first cohort was 40 years (interquartile range 31–52), compared with 46 years (IQR 33–60) in the later group, and this increase was observed across all types of presentation. To avoid multiple testing, the two cohorts were combined into a single datafile (see Table 4.5): adults presenting incidentally were significantly older (median age 48.5 years, IQR 39–59) than those with a symptomatic presentation (median 38 years, IQR 30–53) (Mann-Whitney, $p < 0.001$).

The percentage of women in the first cohort was 59%, but this decreased to 49% in the second, although there was a preponderance of women when the two cohorts were combined (53%).

**Table 4.3 SIVMS 1999-2003: baseline characteristics and events in follow-up**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total n = 136 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (n = 62, 46%) | | Seizure (n = 36, 27%) | | ICH (n = 17, 13%) | | FND (n = 21, 15%) | | | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Age at presentation (median, IQR) | 46 | 34–55 | 34 | 26–46 | 35 | 29–46 | 40 | 32–59 | 40 | 31–52 |
| Sex | | | | | | | | | | |
| Male | 23 | 37% | 22 | 61% | 5 | 29% | 6 | 29% | 56 | 41% |
| Female | 39 | 63% | 14 | 39% | 12 | 71% | 15 | 71% | 80 | 59% |
| Primary CCM location | | | | | | | | | | |
| Lobar | 44 | 71% | 36 | 100% | 7 | 41% | 5 | 24% | 92 | 68% |
| Deep | 4 | 7% | 0 | 0% | 1 | 6% | 4 | 19% | 9 | 7% |
| Cerebellum | 9 | 15% | 0 | 0% | 5 | 29% | 4 | 19% | 18 | 13% |
| Brainstem | 5 | 8% | 0 | 0% | 4 | 24% | 8 | 38% | 17 | 13% |
| Single or multiple CCMs | | | | | | | | | | |
| Single | 56 | 90% | 24 | 67% | 14 | 82% | 18 | 86% | 112 | 82% |
| Multiple | 6 | 10% | 12 | 33% | 3 | 18% | 3 | 14% | 24 | 18% |
| 1st clinical event in follow-up | | | | | | | | | | |
| 1st ICH | 2 | 3% | 0 | 0% | 3 | 18% | 2* | 10% | 7* | 5% |
| 1st FND | 5 | 8% | 1 | 3% | 2 | 12% | 9 | 43% | 17 | 13% |
| No event in 5-year follow-up | 55 | 89% | 35 | 97% | 12 | 71% | 10 | 48% | 112 | 82% |
| Length of censored follow-up (years) (median, IQR) | 5.0 | 5.0–5.0 | 5.0 | 1.4–5.0 | 2.1 | 0.8–5.0 | 3.6 | 0.8–5.0 | 5.0 | 1.6–5.0 |

*One adult experienced an ICH as a second event, having had an FND earlier in follow-up.

**Table 4.4 SIVMS 2006-2010: baseline characteristics and events in follow-up**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total *n* = 165 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (*n* = 68, 41%) | | Seizure (*n* = 52, 32%) | | ICH (*n* = 35, 21%) | | FND (*n* = 10, 6%) | | | |
| | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* |
| Age (median, IQR) | 53 | 42–62 | 37 | 29–51 | 42 | 32–60 | 57 | 52–60 | 46 | 33–60 |
| Sex | | | | | | | | | | |
| Male | 31 | 46% | 32 | 62% | 18 | 51% | 4 | 40% | 85 | 52% |
| Female | 37 | 54% | 20 | 39% | 17 | 49% | 6 | 60% | 80 | 49% |
| Primary CCM location | | | | | | | | | | |
| Lobar | 52 | 77% | 51 | 98% | 18 | 51% | 3 | 30% | 124 | 75% |
| Deep | 1 | 2% | 0 | 0% | 3 | 9% | 0 | 0% | 4 | 2% |
| Cerebellum | 8 | 12% | 0 | 0% | 2 | 6% | 1 | 10% | 11 | 7% |
| Brainstem | 7 | 10% | 1 | 2% | 12 | 34% | 6 | 60% | 26 | 16% |
| Single or multiple CCMs | | | | | | | | | | |
| Single | 58 | 85% | 43 | 83% | 26 | 74% | 9 | 90% | 136 | 82% |
| Multiple | 10 | 15% | 9 | 17% | 9 | 26% | 1 | 10% | 29 | 18% |
| 1st clinical event in follow-up | | | | | | | | | | |
| ICH | 0 | 0% | 1 | 2% | 9 | 26% | 1 | 10% | 11 | 7% |
| FND | 1 | 2% | 1 | 2% | 2 | 6% | 2 | 20% | 6 | 4% |
| No event in follow-up | 67 | 99% | 50 | 96% | 24 | 69% | 7 | 70% | 148 | 90% |
| Length of censored follow-up (years) (median, IQR) | 4.6 | 3.9–5.0 | 5.0 | 4.0–5.0 | 3.4 | 0.3–5.0 | 5.0 | 3.5–5.0 | 4.8 | 3.4–5.0 |

**Table 4.5 SIVMS combined cohorts: baseline characteristics and events in follow-up**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total n = 301 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (n = 130, 43%) | | Seizure (n = 88, 29%) | | ICH (n = 52, 17%) | | FND (n = 31, 10%) | | | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Age at presentation (median, IQR) | 48 | 39–59 | 36 | 26–48 | 38 | 32–57 | 50 | 36–60 | 44 | 32–57 |
| Sex | | | | | | | | | | |
| Male | 54 | 42% | 54 | 61% | 23 | 44% | 10 | 32% | 141 | 47% |
| Female | 76 | 59% | 34 | 39% | 29 | 56% | 21 | 68% | 160 | 53% |
| Primary CCM location | | | | | | | | | | |
| Lobar | 96 | 74% | 87 | 99% | 25 | 48% | 8 | 26% | 216 | 72% |
| Deep | 5 | 4% | 0 | 0% | 4 | 8% | 4 | 13% | 13 | 4% |
| Cerebellum | 17 | 13% | 0 | 0% | 7 | 14% | 5 | 16% | 29 | 10% |
| Brainstem | 12 | 9% | 1 | 1% | 16 | 31% | 14 | 45% | 43 | 14% |
| Single or multiple CCMs | | | | | | | | | | |
| Single | 114 | 88% | 67 | 76% | 40 | 77% | 27 | 87% | 248 | 82% |
| Multiple | 16 | 12% | 21 | 24% | 12 | 23% | 4 | 13% | 53 | 18% |
| 1st clinical event in follow-up | | | | | | | | | | |
| 1st ICH | 2 | 3% | 1 | 1% | 12 | 23% | 3* | 7% | 18* | 6% |
| 1st FND | 6 | 5% | 2 | 2% | 4 | 8% | 11 | 36% | 23 | 8% |
| No event in 5-year follow-up | 122 | 93% | 85 | 97% | 36 | 69% | 17 | 58% | 260 | 86% |
| Length of censored follow-up (years) (median, IQR) | 5.0 | 4.1–5.0 | 5.0 | 3.4–5.0 | 2.6 | 0.4–5.0 | 5.0 | 1.5–5.0 | 5.0 | 2.6–5.0 |

*One adult experienced an ICH as a second event, having had an FND earlier in follow-up.

In both cohorts, however, adults who presented with a seizure tended to be both male and young (under 40 years) (36% in the first cohort and 44% in the second). In the first cohort, 71% of adults presenting with either an ICH or FND were women, but this decreased to 51% in the second cohort. Among the other baseline characteristics, CCM multiplicity was identical in both cohorts (82% had single lesions), and the percentage of brainstem CCMs was similar (13% and 16% respectively). In both cohorts, about 70% of adults with brainstem cavernous malformations presented with either ICH or FND.

The main difference between the two cohorts is the length of available follow-up, which is explored in greater detail in Chapter 7. In the earlier cohort, all adults who were censored at last communication - that is, they experienced neither ICH, FND, interventional treatment, nor death in follow-up – had a minimum of 7.8 years of follow-up (although, as previously stated, in this study five years was stipulated to be the maximum length of follow-up). In the later cohort, the minimum length of follow-up for the equivalent group was 2.2 years; median follow-up was 5.5 years (IQR 4.3 to 7.1 years). However, in Table 4.3, adults in the first cohort presenting with seizure, ICH or FND appear to have less follow-up (lower quartile and median) than those in the second cohort (Table 4.4); this is because more people in the first cohort were censored for interventional treatment (e.g. 29% of those presenting with seizure in the first cohort underwent surgical excision, compared with 6% in the later cohort).

### Brainstem classification compromise

In the 1999–2003 cohort, five of the 17 adults with a brainstem CCM had multiple lesions. Of the five, three presented incidentally and CCM location was designated brainstem because that was a putative predictor. Only one of these three adults experienced an FND in follow-up, which was in fact attributable to the brainstem lesion. In the 2006–2010 cohort, eight of the 26 adults with brainstem CCM had multiple lesions, and again three of these presented incidentally. However, in this cohort, none of these three experienced a clinical event during follow-up.

**Table 4.6 Deaths within five-year follow-up**

| Description | 1999–2003 cohort (*n* = 12) | | 2006–2010 cohort (*n* = 7) | |
|---|---|---|---|---|
| Age at death, median (IQR) | 59.6 | 50–73 | 62.9 | 61–72 |
| Time after presentation (yrs) | 2.0 | 0.9–2.5 | 2.4 | 0.9–4.0 |
| Cause of death | | | | |
| Due to CCM | 3 | 25% | 0 | 0% |
| Due to other cause | 9 | 75% | 5 | 71% |
| Unknown | 0 | 0% | 2 | 29% |
| Interventional treatment in follow-up | 2 | 17% | 0 | 0% |
| ICH in follow-up | 1 | 8% | 0 | 0% |
| FND in follow-up | 2 | 17% | 0 | 0% |
| Sex | | | | |
| Male | 6 | 50% | 3 | 43% |
| Female | 6 | 50% | 4 | 57% |
| Presentation | | | | |
| Incidental | 6 | 50% | 5 | 71% |
| Seizure | 3 | 25% | 1 | 14% |
| ICH or FND | 3 | 25% | 1 | 14% |

## Deaths

In total, 29 people are known to have died since being recruited into the two cohorts: 21 in the earlier cohort and eight in the later. However, 19 people died within the five-year follow-up period: twelve in the earlier group and seven in the later (see Table 4.6). The median age at death was slightly younger for the earlier cohort (59 years, IQR 50–73 years, compared with 62 years, IQR 61–72). Three deaths were due to CCM, fourteen were due to other causes and two causes of death were unknown.

### Subsequent events in untreated follow-up

In the earlier cohort, 136 adults were diagnosed with a cerebral cavernous malformation within the five-year period. During untreated follow-up (to a maximum length of five years) 18 individuals suffered a single clinical event, three experienced two events and one three events. Another adult experienced her fourth event about two months after undergoing a haematoma evacuation (the original planned CCM excision was aborted). The number of events that occurred during untreated follow-up in each cohort, stratified by mode of presentation, is displayed in Table 4.7 below.

Similarly, in the later cohort, 165 adults received a first-ever CCM diagnosis between 2006 and 2010 inclusively, and 17 experienced at least one clinical event in the untreated follow-up period. Again, a few participants experienced subsequent events: two suffered two events and three people had three events (see Table 4.7).

## 4.3.2 ICH attributable to CCM

### First cohort, 1999–2003

In the first cohort, 98 adults presented with a seizure or incidentally (set A in Table 4.1 and 4.9; see the first analysis in Table 4.8, and the flowchart in Figure 4.3). Of these, two adults who presented incidentally suffered a haemorrhage attributable to the CCM during the five-year follow-up period (one of which was fatal). The Kaplan-Meier estimated five-year risk of a first intracranial haemorrhage, attributable to a CCM, among those who presented incidentally or with a seizure was 2.4% (95% CI 0% to 5.7%).

Set C in Tables 4.1 and 4.9 consists of the two adults with non-haemorrhagic presentation who suffered a first ICH in follow-up, and two adults who presented with a focal neurological deficit and also had a similar ICH in follow-up, together with the 17 who initially presented with a haemorrhage. The adults in set C are included in the estimated risk of a second ICH attributable to CCM during follow-up (see Table 4.8).

**Table 4.7 Clinical events in untreated follow-up**

| Original mode of presentation | 1st event after presentation | 2nd event after presentation | 3rd event after presentation | 4th event after presentation |
|---|---|---|---|---|
| ***SIVMS, 1999–2003*** | | | | |
| **60 incidental** | 1 ICH* *(fatal)* | | | |
| | 1 ICH* | 1 ICH* | | |
| | 1 FND* | | | |
| | 4 FND† | 1 FND† | | |
| **2 FND†** | | | | |
| **36 seizures** | 1 FND† | | | |
| **21 FND*** | 1 ICH* | 1 ICH* | | |
| | 8 FND* | 1 ICH* | 1 ICH* | 1 FND* |
| | 1 FND† | | | |
| **17 ICH*** | 3 ICH* | 1 ICH* | 1 FND† | |
| | 2 FND* | | | |
| ***SIVMS, 2006–2010*** | | | | |
| **66 incidental** | 1 FND† | 1 FND† | 1 FND† | |
| **2 FND†** | | | | |
| **52 seizures** | 1 ICH* | | | |
| | 1 FND† | | | |
| **10 FND*** | 1 ICH* | 1 FND* | | |
| | 1 FND* | | | |
| | 1 FND† | | | |
| **35 ICH*** | 9 ICH* | 2 ICH* | 1 FND* | |
| | 1 FND* | | | |
| | 1 FND† | 1 FND† | 1 FND† | |

**Notes**

*Event definitely attributable to CCM. †Event possibly attributable to CCM.

**Table 4.8 Composition of datafiles used for analyses of untreated clinical course**

| Analysis | Cohort | Included | $n_{included}$ | Set | Event in follow-up | $n_{events}$ | Outcome |
|---|---|---|---|---|---|---|---|
| **ICH due to CCM** | SIVMS, 1999–2003 | Incidental + seizure presentation | 98 | A | 1st ICH | 2 | 1st ICH |
| | | ICH presentation | 17 | C | 1st ICH | 3 | 2nd ICH |
| | | Incidental*, seizure* + FND presentation, with a 1st ICH in follow-up | 4† | C | 2nd ICH | 3 | 2nd ICH |
| | | **Total** | **119†** | | | **8** | |
| **ICH due to CCM** | SIVMS, 2006–2010 | Incidental + seizure presentation | 120 | E | 1st ICH | 1 | 1st ICH |
| | | ICH presentation | 35 | G | 1st ICH | 9 | 2nd ICH |
| | | Incidental*, seizure* + FND presentation, with a 1st ICH in follow-up | 2 | G | 2nd ICH | 0 | 2nd ICH |
| | | **Total** | **157** | | | **10** | |
| **ICH/FND due or possibly due to CCM** | SIVMS, 1999–2003 | Incidental + seizure presentation | 98 | B | 1st ICH/FND | 8 | 1st clinical event |
| | | ICH + FND presentation | 38 | D | 1st ICH/FND | 15 | 2nd clinical event |
| | | FND possibly due to CCM presentation* | 2 | D | 1st ICH/FND | 0 | 2nd clinical event |
| | | Incidental* + seizure* presentation, with a 1st ICH/FND in follow-up | 8† | D | 2nd ICH/FND | 2 | 2nd clinical event |
| | | **Total** | **144†** | | | **25** | |
| **ICH/FND due or possibly due to CCM** | SIVMS, 2006–2010 | Incidental + seizure presentation | 118 | F | 1st ICH/FND | 3 | 1st clinical event |
| | | ICH + FND presentation | 45 | H | 1st ICH/FND | 14 | 2nd clinical event |
| | | FND possibly due to CCM presentation* | 2 | H | 1st ICH/FND | 0 | 2nd clinical event |
| | | Incidental* + seizure* presentation, with a 1st ICH/FND in follow-up | 3 | H | 2nd ICH/FND | 1 | 2nd clinical event |
| | | **Total** | **168** | | | **18** | |

**These adults are re-entered into the analysis with a different outcome.* †*Includes adult who presented incidentally and had a fatal first ICH 2 years later.*

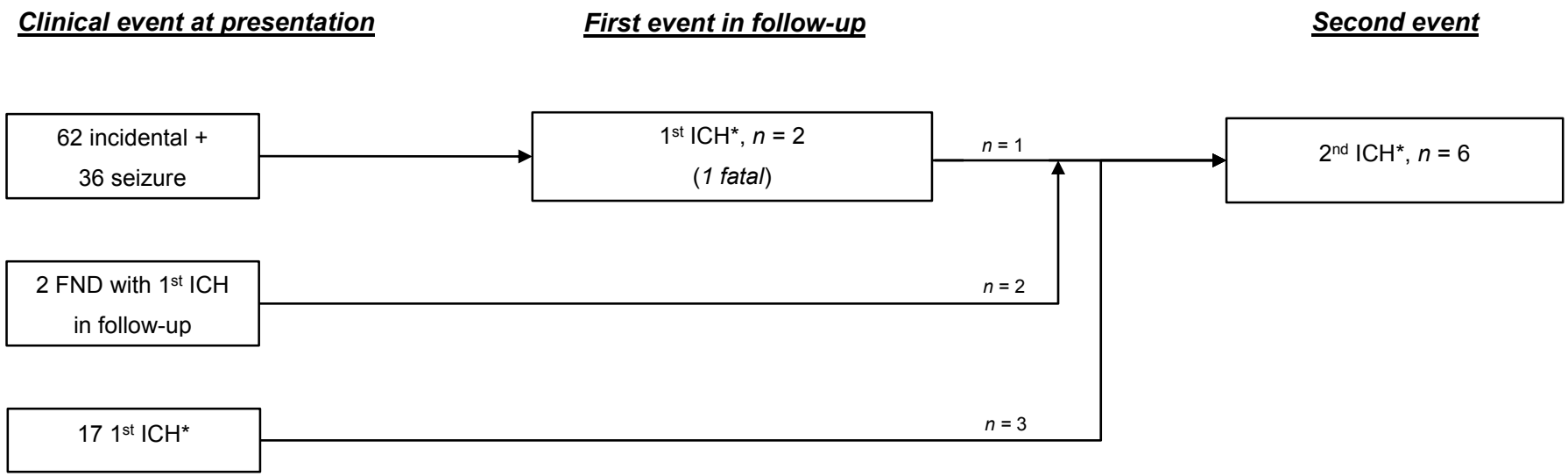



**Figure 4.3 Flowchart showing which adults in the first cohort entered the analysis of first ICH definitely attributable to CCM**

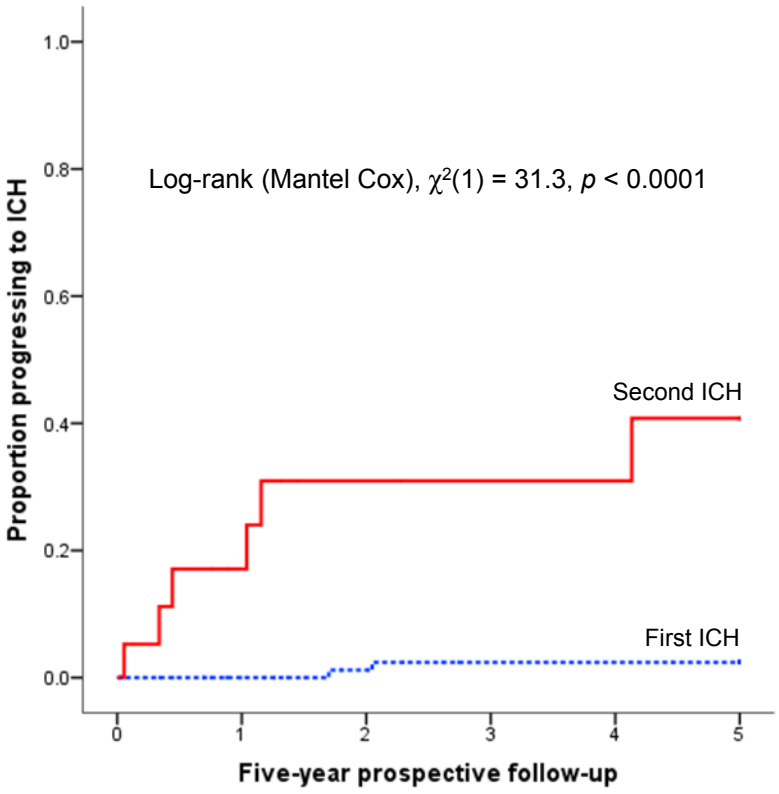
Six adults suffered a second ICH during the five-year follow-up period: three adults who presented with an ICH, one who presented incidentally and two who presented with FND. The Kaplan-Meier estimated five-year risk of a second ICH was 40.8% (95% CI 14.2% to 67.3%).

If the two adults who presented with FND are excluded from the analysis to second ICH (on the grounds that the 21 adults who presented with an FND might in reality have had an ICH, and therefore should be excluded from the analysis, due to uncertainty), then four recurrent ICH occurred, and the Kaplan-Meier estimated risk of a second ICH definitely due to CCM decreases to 31.9% (95% CI 4.5% to 59.3%).

In Figure 4.4, a Kaplan-Meier plot displays the estimated progression to first or second intracranial haemorrhage definitely attributable to CCM within five years of untreated follow-up. As can be observed, the risk of a second ICH is significantly greater than that of a first ICH (log-rank $\chi^2(1) = 31.3$, $p < 0.0001$). Of the eight haemorrhages that occurred during follow-up, one was fatal; this occurred to a 50-year-old man with a single lesion in the lobar region of the brain, who had presented incidentally two years previously.

**Table 4.9 Number of adults and outcomes in follow-up for each set**

| Presentation: / Outcome: | Incidental + seizure presentation | | ICH presentation or in follow-up | ICH + FND presentation or in follow-up |
|---|---|---|---|---|
| Cohort | 1st ICH | 1st ICH + FND | Recurrent ICH | Recurrent ICH + FND |
| **Cohort 1** | **set A** | **set B** | **set C** | **set D** |
| 1999–2003 | *n* = 98 | *n* = 96 | *n* = 21 | *n* = 48 |
| | 2 ICH | 2 ICH + 6 FND | 6 ICH | 5 ICH + 12 FND |
| **Cohort 2** | **set E** | **set F** | **set G** | set H |
| 2006–2010 | *n* = 120 | *n* = 118 | *n* = 37 | n = 50 |
| | 1 ICH | 1 ICH + 2 FND | 9 ICH | 10 ICH + 5 FND |




| Number of adults at risk (number of ICH in preceding year) | | | | | | |
|---|---|---|---|---|---|---|
| **First ICH** | 98 | 88(0) | 82(1) | 77(1) | 77(0) | 76(0) |
| **Second ICH** | 21 | 12(3) | 8(2) | 7(0) | 7(0) | 6(1) |

**Figure 4.4 Kaplan-Meier plot of estimated progression to first or second intracranial haemorrhage definitely attributable to CCM in untreated follow-up of SIVMS cohort, 1999–2003**

## Second cohort, 2006–2010

Of 120 adults with non-haemorrhagic presentation in the later cohort, a man who presented with a seizure was the only adult to experience a haemorrhage due to CCM during follow-up (set E in Tables 4.1 and 4.9; see second analysis in Table 4.8 and Figure 4.5). The Kaplan-Meier estimated five-year risk of a first ICH due to CCM was 0.9% (95% CI 0% to 2.6%).

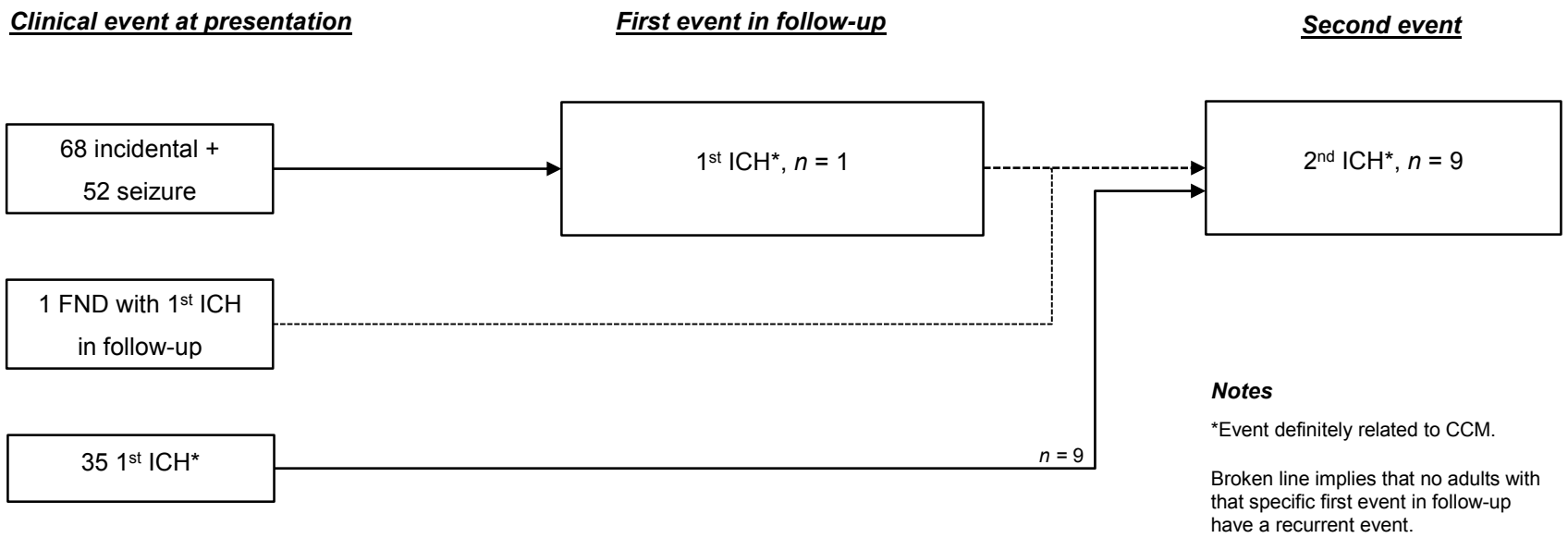
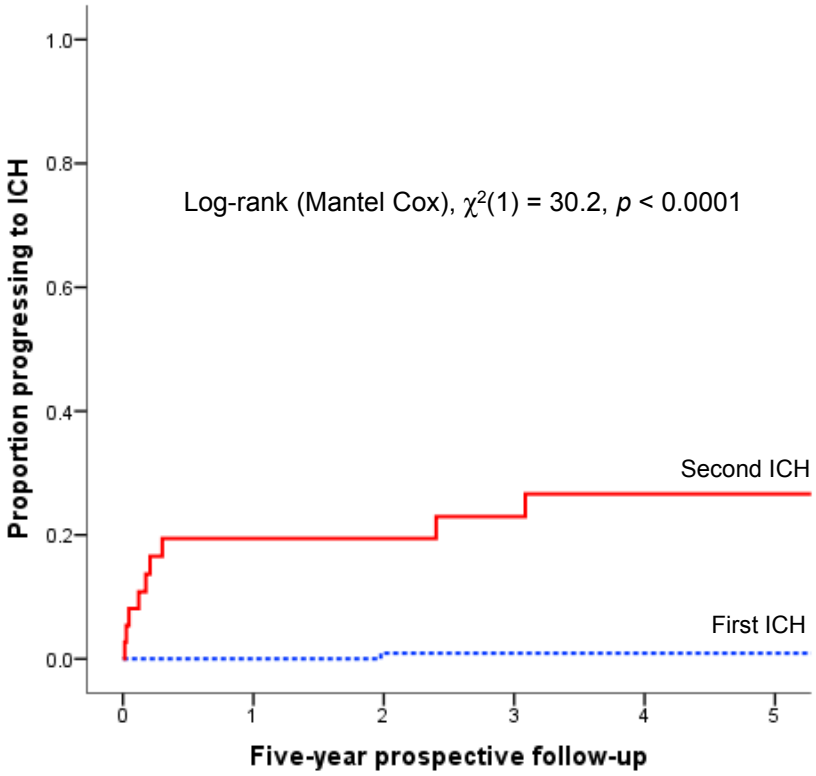



**Figure 4.5 Flowchart showing which adults in the second cohort entered the analysis of first ICH definitely attributable to CCM**

In this cohort, a woman who presented with an FND and suffered an ICH due to CCM in follow-up, together with the man who had a first ICH after seizure presentation, were included with the 35 adults with initial ICH presentation in the analysis to second ICH due to CCM (set G in Tables 4.1 and 4.9; see the second analysis in Table 4.8 above, and the flowchart in Figure 4.5). Nine participants, all of whom presented with an ICH, suffered a subsequent ICH due to CCM within five years of presentation; two of these adults had a subsequent haemorrhage later in follow-up (see Table 4.7 above). No haemorrhage in this cohort was fatal. The Kaplan-Meier estimated five-year risk of a recurrent ICH due to CCM during untreated follow-up was 26.6% (95% CI 11.5% to 41.8%); if the adult who presented with an FND and suffered an ICH in follow-up is removed from the analysis, this estimate increases to 27.1% (95% CI 11.8% to 42.5%).

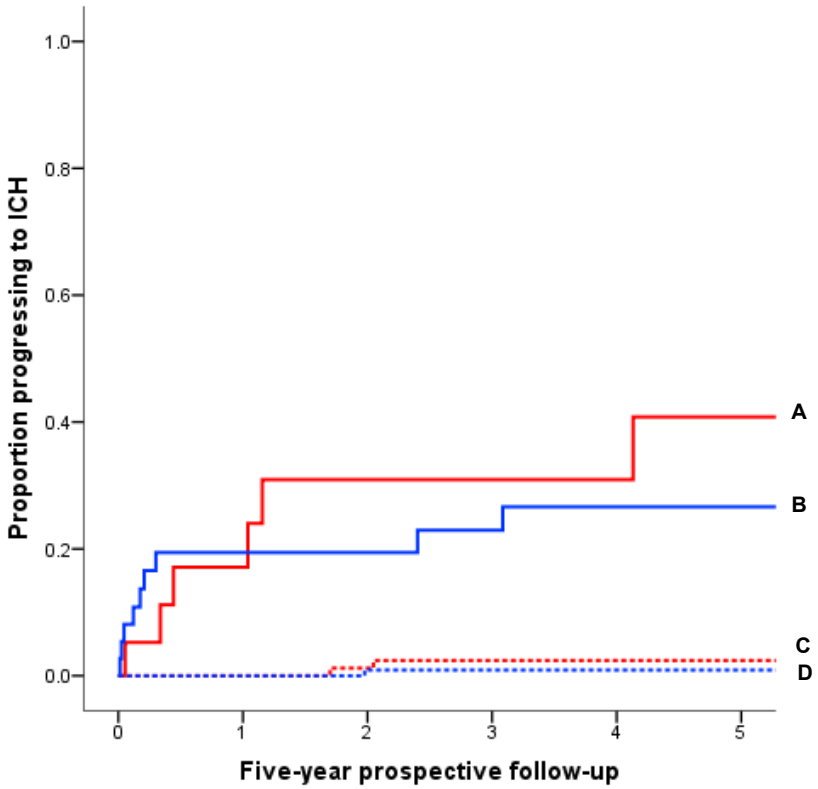
A Kaplan-Meier plot of the progression to first and second ICH is presented in Figure 4.6; again, the estimated risk of a second ICH is significantly greater than that of a first (log-rank $\chi^2(1) = 30.2$, $p < 0.0001$).

In Figure 4.7, the Kaplan-Meier plots for the two cohorts are combined. It should be borne in mind that 53 people in the second cohort (34% of adults included in this analysis) have less than five years follow-up, due to the recruitment period of the cohort; however, only three adults have less than 2.5 years follow-up, and most outcomes tend to occur in the first half of the follow-up period. In addition, three people (two from the first cohort and one from the second) have been re-entered into the analysis, as they presented with a seizure or incidentally, suffered a first ICH, and then were included in the second ICH analysis (see Table 4.8, and Figures 4.3 and 4.5). The plots for both analyses are very similar; about 5% of each cohort suffers a recurrent haemorrhage within five years of follow-up.




| Number of adults at risk (number of ICH in preceding year) | | | | | | |
|---|---|---|---|---|---|---|
| **First ICH** | 120 | 115(0) | 111(1) | 107(0) | 91(0) | 63(0) |
| **Second ICH** | 37 | 25(7) | 23(0) | 21(1) | 19(1) | 12(0) |

**Figure 4.6 Kaplan-Meier plot of progression to first or second ICH definitely due to CCM in SIVMS cohort 2006–2010**




**Number of adults at risk (number of ICH in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **A** | 21 | 12(3) | 8(2) | 7(0) | 7(0) | 6(1) |
| **B** | 37 | 25(7) | 23(0) | 21(1) | 19(1) | 12(0) |
| **C** | 98 | 88(0) | 82(1) | 77(1) | 77(0) | 76(0) |
| **D** | 120 | 115(0) | 111(1) | 107(0) | 91(0) | 63(0) |

| | |
|---|---|
| **A** | **1999–2003 cohort, 2nd ICH** |
| **B** | **2006–2010 cohort, 2nd ICH** |
| **C** | **1999–2003 cohort, 1st ICH** |
| **D** | **2006–2010 cohort, 1st ICH** |

**Figure 4.7 Kaplan-Meier plot of progression to first or second ICH definitely due to CCM, stratified by SIVMS cohort**

### 4.3.3 Clinical event due or possibly due to CCM

The outcome in the following two subsections is either intracranial haemorrhage or focal neurological deficit that is definitely or possibly attributable to CCM; it is referred to as clinical event in the text. Clinical event is the primary outcome in this chapter, as it is arguably of most relevance to patients: the level of functional impairment after an FND can be equally as severe as after an ICH and, as has been mentioned earlier, it is also possible that some events in the cohorts that were recorded as FND would have been recorded as ICH, had appropriate neuro-imaging been performed at the appropriate time.

#### First cohort, 1999–2003

In the first cohort, 98 adults presented with a seizure or incidentally, eight of whom then suffered a first clinical event within the five-year follow-up period (two ICH and six FND) (set B in Tables 4.1 and 4.9; see third analysis in Table 4.8 above, and Figure 4.8). These eight, together with two adults who were recorded as incidental, since their FND symptoms at presentation were only possibly due to CCM, plus the 38 adults who presented with an ICH or FND were included in the analysis to second clinical event in follow-up (set D in Tables 4.1 and 4.9). In this group there were 17 clinical event outcomes: five ICH, six FND and six non-haemorrhagic FND.

The Kaplan-Meier estimated five-year risk of a first clinical event, due or possibly due to CCM, among those with seizure or incidental presentation was 9.4% (95% CI 3.2% to 15.6%), and the similar risk of a second clinical event among those who had suffered a prior event at presentation or follow-up was 42.2% (95% CI 26.7% to 57.7%). As can be observed in the Kaplan-Meier plot (see Figure 4.9), the risk of a clinical event within five years of presentation was significantly greater for those who had already experienced a clinical event at presentation or earlier in follow-up (log-rank $\chi^2(1) = 20.2$, $p < 0.0001$).

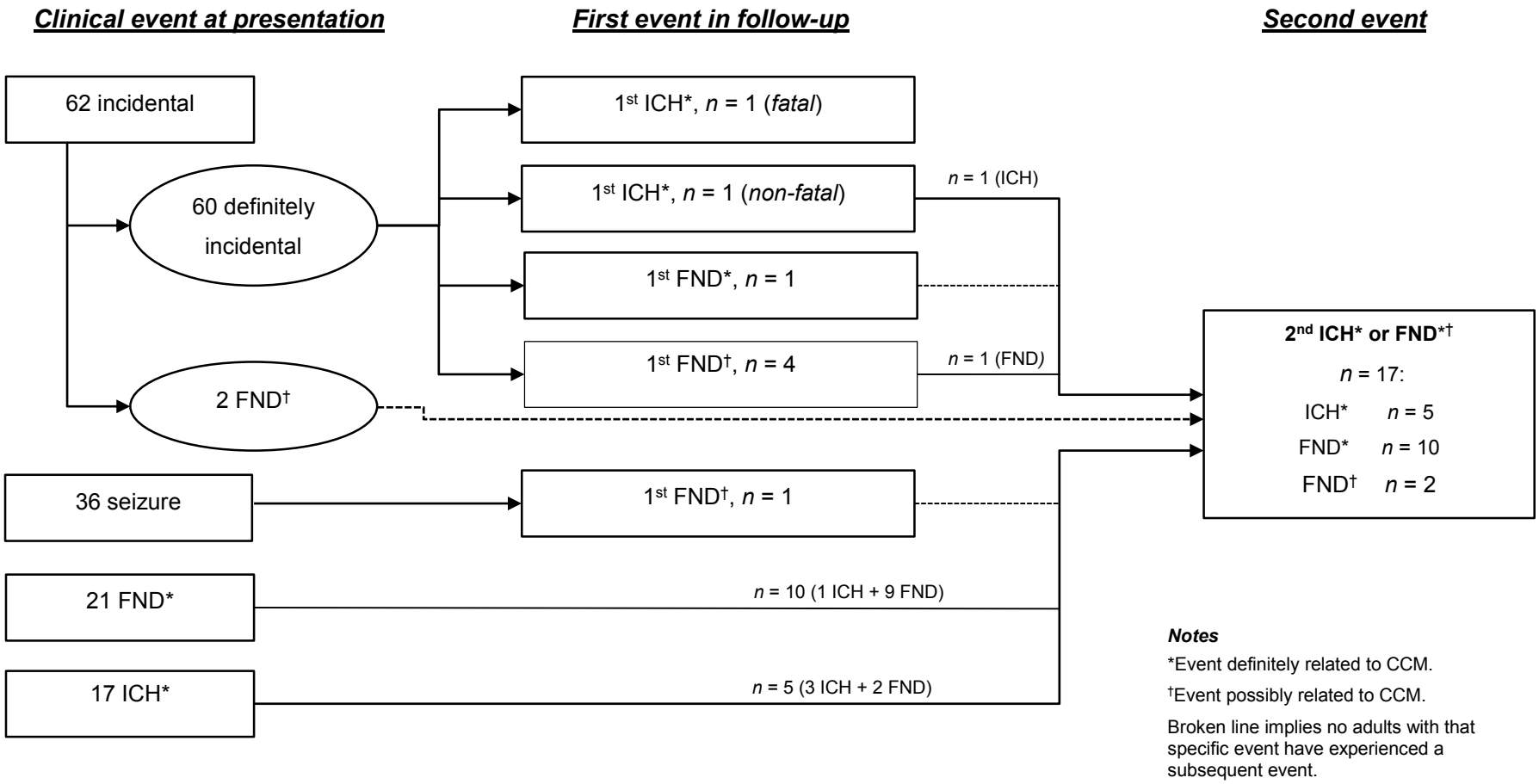
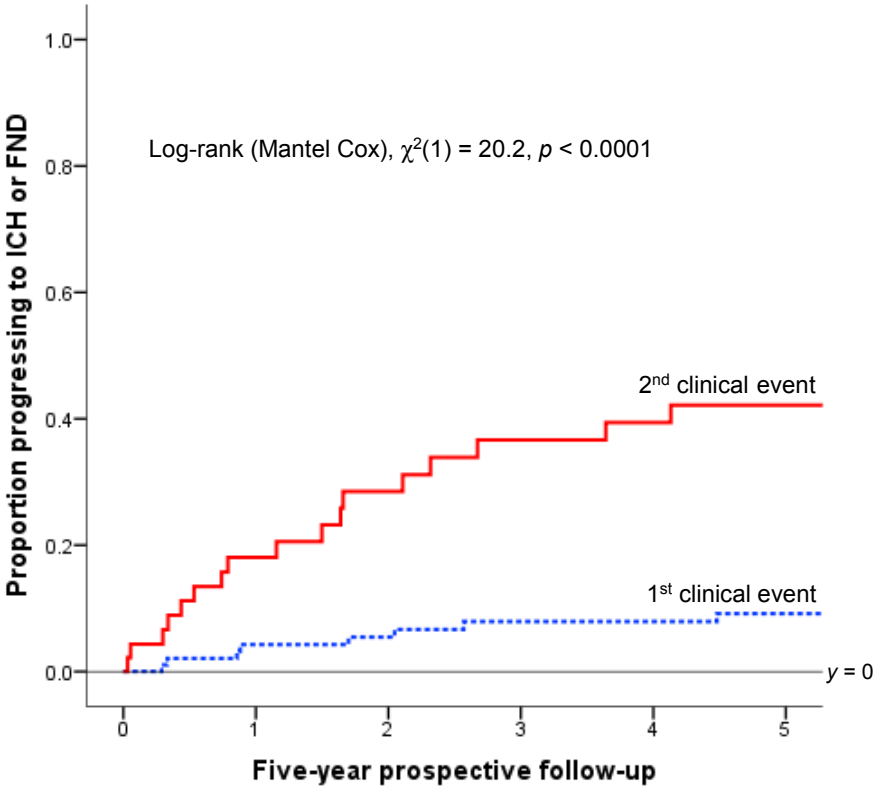



**Figure 4.8 Flowchart showing which patients in SIVMS, 1999–2003 were included in the recurrent ICH or FND definitely or possibly attributable to CCM**




| Number of adults at risk (number of ICH or FND in preceding year) | | | | | | |
|---|---|---|---|---|---|---|
| **1st clinical event** | 96 | 83(4) | 77(1) | 71(2) | 71(0) | 70(1) |
| **2nd clinical event** | 48 | 33(8) | 27(4) | 23(3) | 22(1) | 20(1) |

**Figure 4.9 Kaplan-Meier estimate of progression to first or second intracranial haemorrhage or focal neurological deficit, definitely or possibly due to CCM, in SIVMS, 1999–2003**

### Second cohort, 2006–2010

Of 118 adults who presented with a seizure or incidentally, three suffered a first clinical event due or possibly due to CCM within five years of presentation (set F in Tables 4.1 and 4.9; see final analysis in Table 4.8 above, and Figure 4.10 below). These three adults joined the two who were recorded as incidental presentation, but had a focal neurological deficit that was possibly due to the CCM, and the 45 who presented with a haemorrhage or FND that was due to the CCM as the included participants for a second outcome (set H in Tables 4.1. and 4.9). In this group of 50 adults, fifteen experienced a second clinical event (ten ICH, two FND and three non-haemorrhagic FND).

The Kaplan-Meier estimated risk of a first clinical event due or possibly due to a CCM within five years of untreated follow-up for an individual presenting initially with a seizure or incidentally was 2.7% (95% CI 0% to 5.7%); a similar risk for an individual who had already experienced a clinical event due or possibly due to a CCM at presentation or during earlier follow-up was 33.5% (95% CI 19.5% to 47.5%). The Kaplan-Meier plot for estimated progression to a first or second clinical event is displayed in Figure 4.11; the estimated risk of a subsequent clinical event is significantly higher than the risk of a first event in follow-up (log-rank, $\chi^2(1) = 31.7$, $p < 0.0001$).

### Summary

In Figure 4.12, the Kaplan-Meier plots for both cohorts are displayed. The Kaplan-Meier estimated annual risk of either an intracranial haemorrhage or clinical event for both cohorts is presented in Table 4.10. Broadly speaking, the hazard rate for both ICH and clinical event tends to diminish after the first three years of follow-up; however, it is not yet known whether this trend continues in the long term.

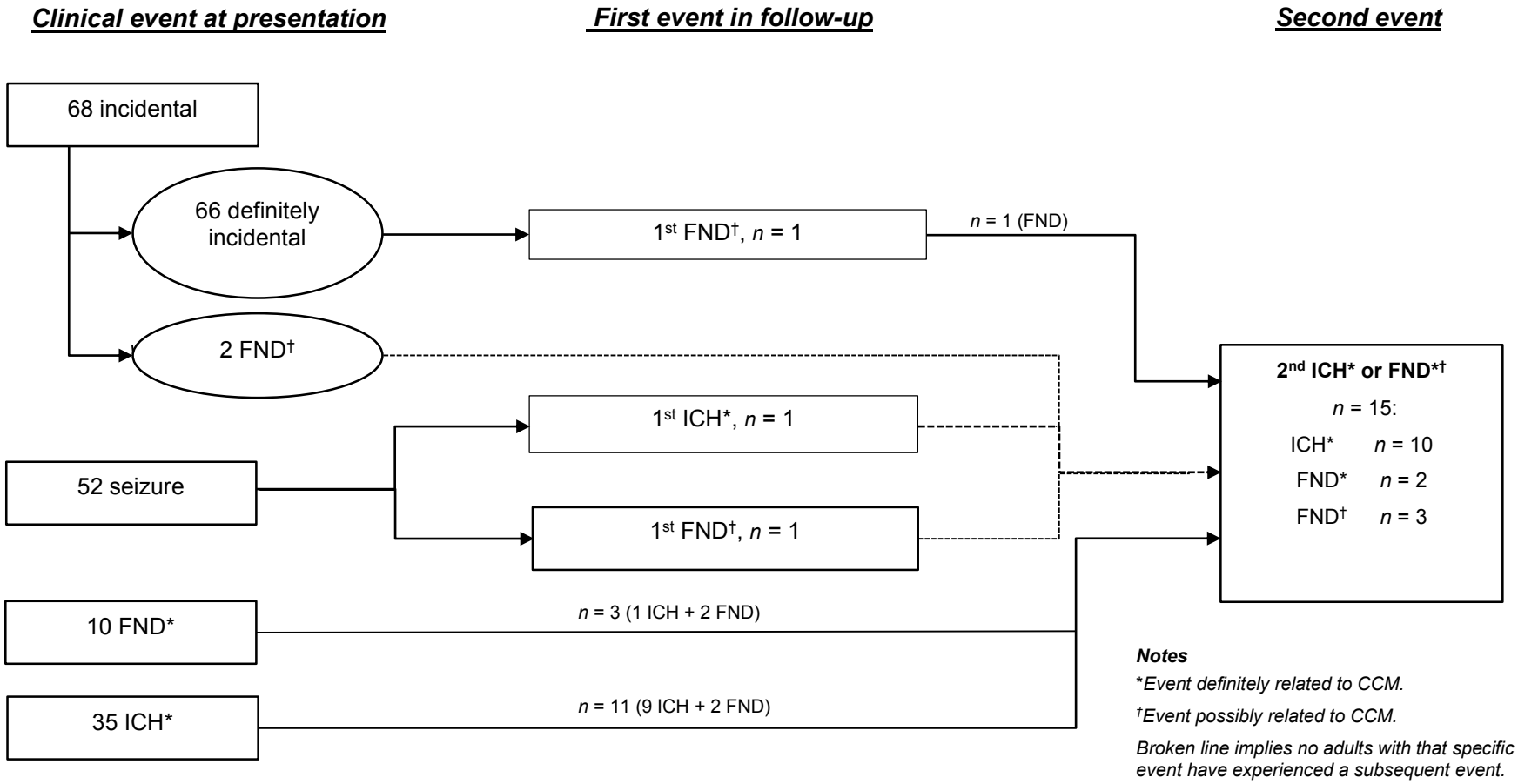
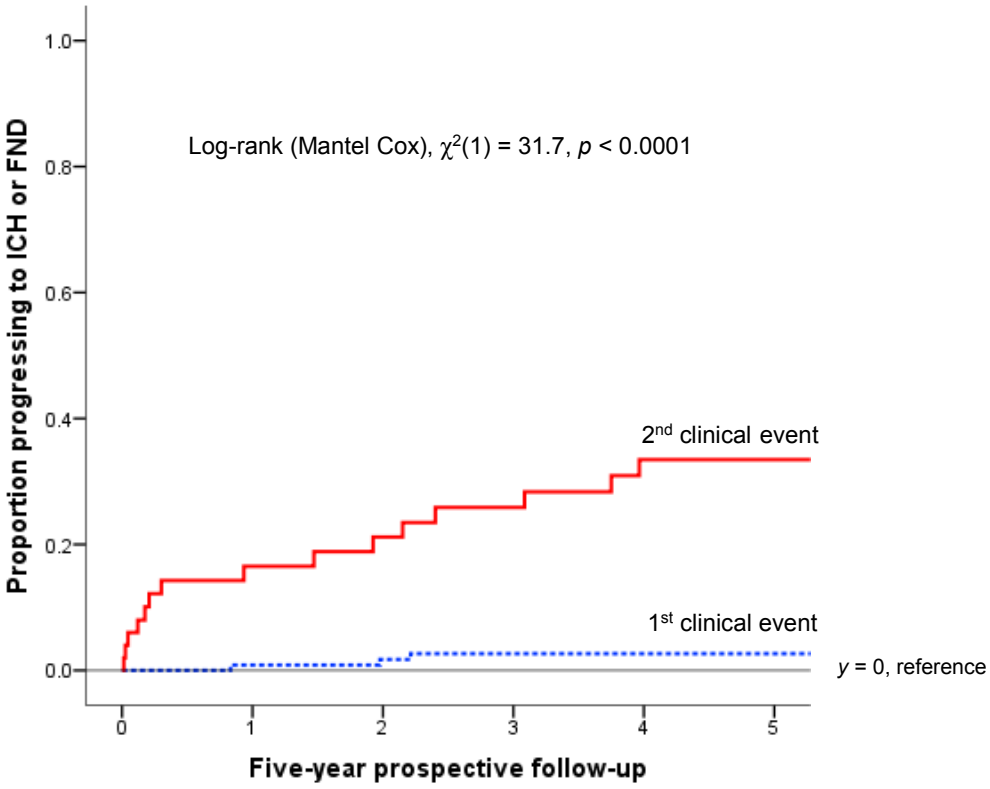
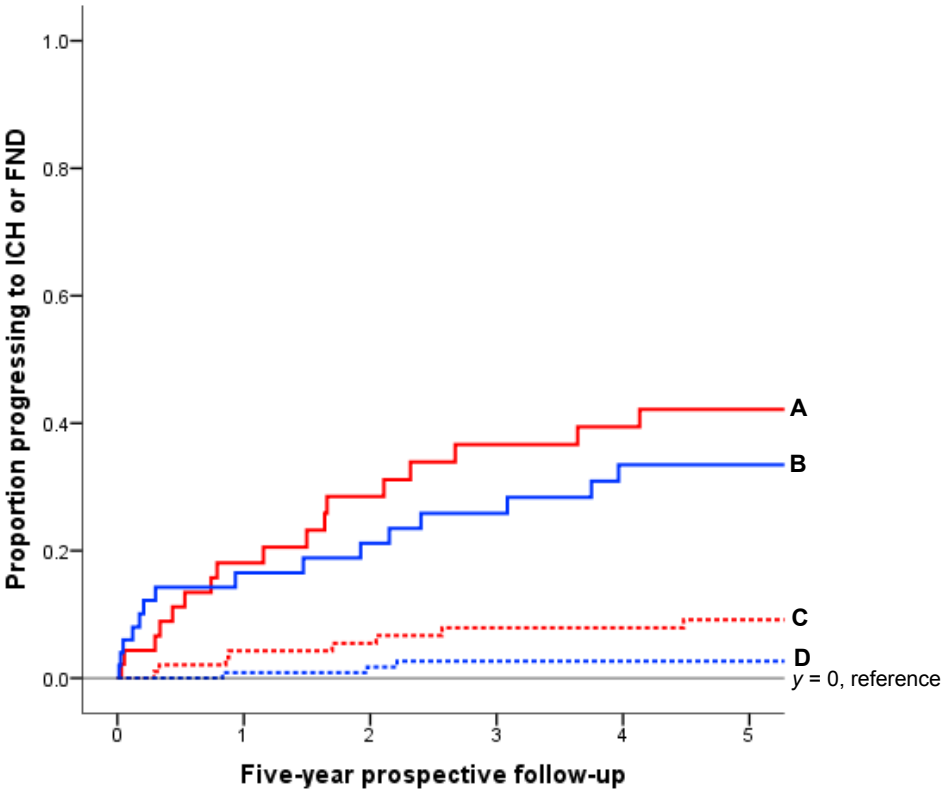



**Figure 4.10 Flowchart showing which patients in SIVMS, 2006–2010 were included in the recurrent ICH or FND definitely or possibly attributable to CCM**




| Number of adults at risk (number of ICH or FND in preceding year) | | | | | | |
|---|---|---|---|---|---|---|
| **1st clinical event** | 118 | 112(1) | 108(1) | 104(1) | 88(0) | 61(0) |
| **2nd clinical event** | 50 | 37(8) | 34(2) | 30(2) | 25(3) | 17(0) |

**Figure 4.11 Kaplan-Meier estimate of progression to first or second intracranial haemorrhage or focal neurological deficit, definitely or possibly due to CCM, in SIVMS, 2006–2010**




**Number of adults at risk (number of ICH or FND in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **A** | 48 | 33(8) | 27(4) | 23(3) | 22(1) | 20(1) |
| **B** | 50 | 37(8) | 34(2) | 30(2) | 25(3) | 17(0) |
| **C** | 96 | 83(4) | 77(1) | 71(2) | 71(0) | 70(1) |
| **D** | 118 | 112(1) | 108(1) | 104(1) | 88(0) | 61(0) |

| | |
|---|---|
| **A** | **1999–2003 cohort, 2nd ICH or FND** |
| **B** | **2006–2010 cohort, 2nd ICH or FND** |
| **C** | **1999–2003 cohort, 1st ICH or FND** |
| **D** | **2006–2010 cohort, 1st ICH or FND** |

**Figure 4.12 Kaplan-Meier plot of estimated progression to first or second clinical event definitely or possibly due to CCM, stratified by SIVMS cohort**

**Table 4.10 Annual estimated risk of outcome events within five years of presentation**

| Analysis | Year | SIVMS, 1999–2003 | | SIVMS, 2006–2010 | |
|---|---|---|---|---|---|
| | | Hazard rate | 95% CI | Hazard rate | 95% CI |
| ***ICH only*** | | | | | |
| **1st ICH** | 1 | - | | - | |
| | 2 | 1.2 | 0 to 3.5 | 0.9 | 0 to 2.6 |
| | 3 | 1.3 | 0 to 3.7 | - | |
| | 4 | - | | - | |
| | 5 | - | | - | |
| **2nd ICH** | 1 | 18.2 | 0 to 38.7 | 22.6 | 6.0 to 39.2 |
| | 2 | 20.0 | 0 to 47.6 | - | |
| | 3 | - | | 4.5 | 0 to 13.5 |
| | 4 | - | | 5.0 | 0 to 14.8 |
| | 5 | 15.4 | 0 to 45.4 | - | |
| ***Clinical event*** | | | | | |
| **1st clinical event** | 1 | 4.5 | 0.1 to 8.8 | 0.9 | 0 to 2.6 |
| | 2 | 1.3 | 0 to 3.7 | 0.9 | 0 to 2.7 |
| | 3 | 2.7 | 0 to 6.4 | 0.9 | 0 to 2.8 |
| | 4 | - | | - | |
| | 5 | 1.4 | 0 to 4.2 | - | |
| **2nd clinical event** | 1 | 19.8 | 6.1 to 33.4 | 18.4 | 5.7 to 31.1 |
| | 2 | 13.3 | 0.3 to 26.4 | 5.6 | 0 to 13.4 |
| | 3 | 12.0 | 0 to 25.6 | 6.3 | 0 to 14.9 |
| | 4 | 4.4 | 0 to 13.2 | 10.9 | 0 to 23.2 |
| | 5 | 4.8 | 0 to 14.1 | - | |

### 4.3.4 Putative predictors of clinical event

At the time of data extraction, sex and CCM location were proposed as putative predictors of clinical event, since there were insufficient outcomes in each cohort to support more than two covariates (Harrell et al., 1984, Concato et al., 1995, Peduzzi et al., 1995). Cox regression analysis was not possible because the proportional hazards assumption did not hold; however, exploratory univariate analyses were performed to investigate the effect of sex and brainstem on progression to second clinical event.

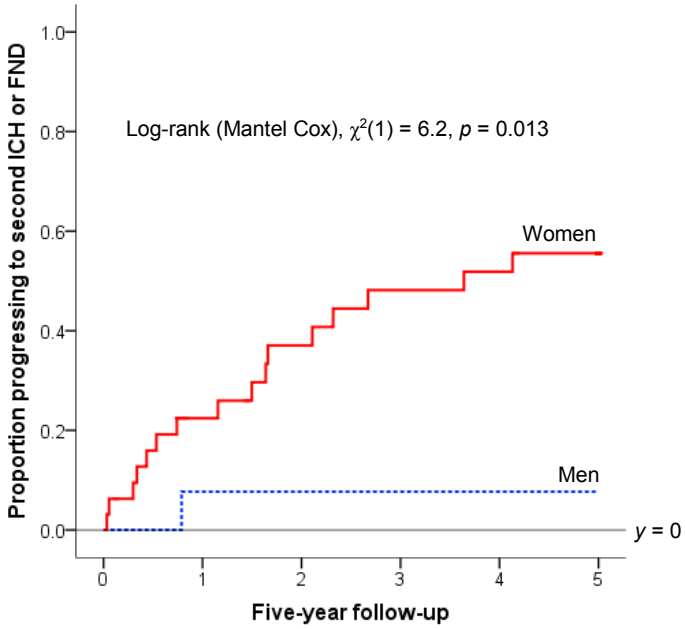
#### Sex

In the earlier cohort, 32 women and 16 men experienced a first clinical event; of the 17 recurrent events within five years of presentation, 16 occurred to women. The Kaplan-Meier estimated five-year risk of a recurrent clinical event for women diagnosed with CCM who had either presented with a clinical event or experienced one in follow-up was 55.6% (95% CI 37.1% to 74.0%), compared with a similar estimated five-year risk for men of 7.7% (95% CI 0% to 22.2%) (see Table 4.11).

**Table 4.11 Kaplan-Meier estimated five-year risk of a recurrent clinical event**

| | 5-year risk | | | 5-year risk | |
|---|---|---|---|---|---|
| **Sex** | **Estimate (%)** | **95% CI (%)** | **CCM location** | **Estimate (%)** | **95%CI (%)** |
| **1999–2003** | | | | | |
| Female | 55.6 | 37.1 to 74.0 | Brainstem | 57.1 | 31.2 to 83.1 |
| Male | 7.7 | 0.0 to 22.2 | Other location | 33.7 | 15.3 to 52.2 |
| **2006–2010** | | | | | |
| Female | 34.8 | 13.7 to 55.9 | Brainstem | 64.5 | 40.9 to 88.1 |
| Male | 32.4 | 13.7 to 51.0 | Other location | 13.6 | 1.1 to 26.0 |
| **Both cohorts** | | | | | |
| Female | 47.0 | 32.8 to 61.2 | Brainstem | 60.8 | 43.4 to 78.2 |
| Male | 24.2 | 10.3 to 38.1 | Other location | 23.4 | 12.1 to 34.8 |

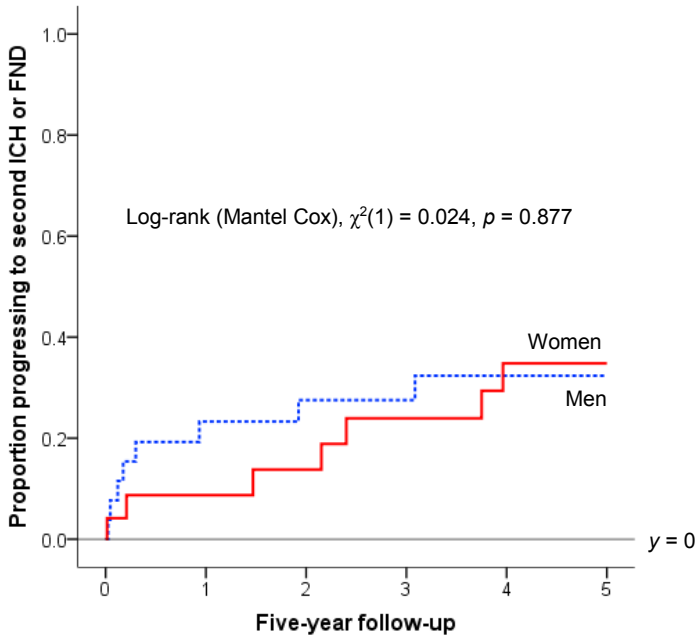
**(A)**




**Number of adults at risk (number of ICH or FND in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Women** | 32 | 22(7) | 17(4) | 14(3) | 13(1) | 11(1) |
| **Men** | 16 | 11(1) | 10(0) | 9(0) | 9(0) | 9(0) |

**(B)**



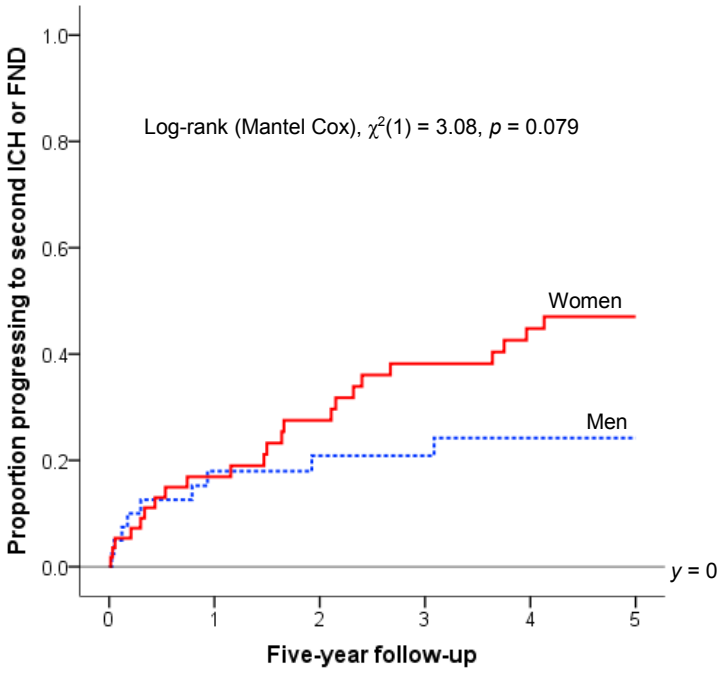

**Number of adults at risk (number of ICH or FND in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Women** | 24 | 18(2) | 17(1) | 15(2) | 12(2) | 9(0) |
| **Men** | 26 | 19(6) | 17(1) | 15(0) | 13(1) | 8(0) |

**Figure 4.13 Kaplan-Meier plots showing estimated progression to second ICH or FND, stratified by sex: (A) 1999–2003 cohort and (B) 2006–2010 cohort**

Thus, in the earlier cohort, women had a significantly greater estimated risk of a recurrent clinical event (log-rank, $\chi^2(1) = 6.2$, $p = 0.013$); this is demonstrated graphically in the Kaplan-Meier plot in Figure 4.13(A). This increased risk, however, was not observed in the later cohort: here, 24 women and 26 men experienced a first event, and 7 women and 8 men suffered a recurrence (see Figure 4.13(B) and Table 4.11). The corresponding Kaplan-Meier estimated five-year risks of a recurrent clinical event were 34.8% (95% CI 13.7% to 55.9%) for women and 32.4% (95% CI 13.7 to 51.0%) for men.

When the two cohorts were pooled, 23 women (of 56 who had experienced at least one clinical event) suffered a recurrence compared with nine men (of 42). The corresponding Kaplan-Meier estimated five-year risks for women and men were 47.0% (95% CI 32.8% to 61.2%) and 24.2% (95% CI 10.3% to 38.1%) respectively (Figure 4.14 and Table 4.11). Although women in the pooled SIVMS cohorts had a greater estimated risk of recurrence than men, this increased risk did not achieve statistical significance (log-rank, $\chi^2(1) = 3.1$, $p = 0.079$).




**Number of adults at risk (number of ICH or FND in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Women** | 56 | 40(9) | 34(5) | 29(5) | 25(3) | 20(1) |
| **Men** | 42 | 30(7) | 27(1) | 24(0) | 22(1) | 17(0) |

**Figure 4.14 Kaplan-Meier plot showing estimated progression to second ICH or FND, stratified by sex: both cohorts**

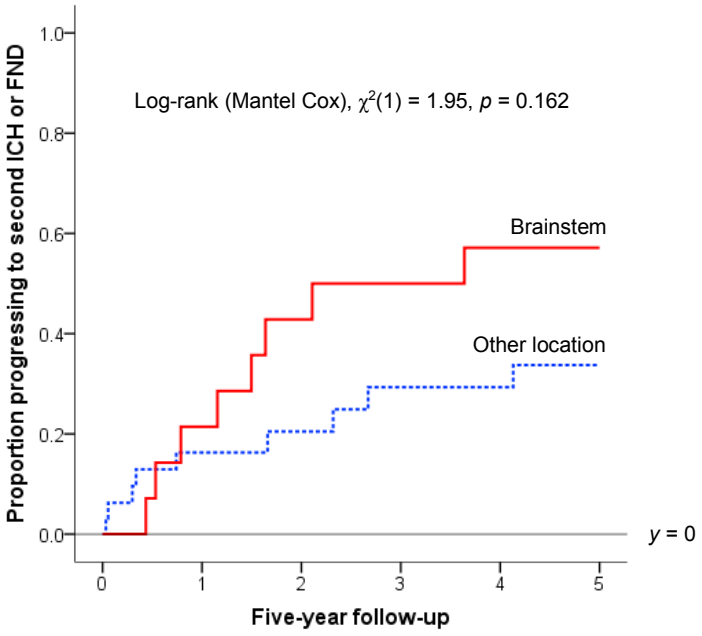
### CCM location

Of the 48 individuals in the earlier cohort who experienced a first clinical event at presentation or during follow-up, 14 adults had a brainstem CCM and 34 had a lesion in another location; eight participants with a brainstem CCM and nine with a CCM in a different area of the brain suffered a recurrence within five years of presentation (see Figure 4.15 (A) and Table 4.11). Although the Kaplan-Meier estimated risk of a second clinical event was increased for those with brainstem cavernomas in this cohort, this increase did not achieve statistical significance (log-rank $\chi^2(1) = 2.0$, $p = 0.162$). The Kaplan-Meier five-year estimated risk for a second clinical event for adults with a brainstem lesion was 57.1% (95% CI 31.2% to 83.1%), and the corresponding risk for adults with a non-brainstem lesion was 33.7% (95% CI 15.3% to 52.2%).

In the later cohort, 11 of the 19 adults with brainstem lesions suffered a recurrence, compared with four of the 31 with lesions in other locations (see Figure 4.15 (B)). Those who harboured a brainstem CCM had an increased risk of a recurrent clinical event (log-rank $\chi^2(1) = 10.0$, $p = 0.002$): the Kaplan-Meier five-year estimated risk of a recurrence for an adult with a brainstem CCM was 64.5% (95% CI 40.9% to 88.1%), and a similar risk for a non-brainstem CCM was 13.6% (95% CI 1.1% to 26.0%) (see Table 4.11).

When both cohorts were pooled, 19 of the 33 participants with brainstem CCMs experienced a second event, compared with 13 of the 65 adults with lesions in other parts of the brain. As can be observed in Figure 4.16, those with a brainstem lesion had an increased risk of suffering a recurrent clinical event (log-rank $\chi^2(1) = 10.3$, $p = 0.001$).

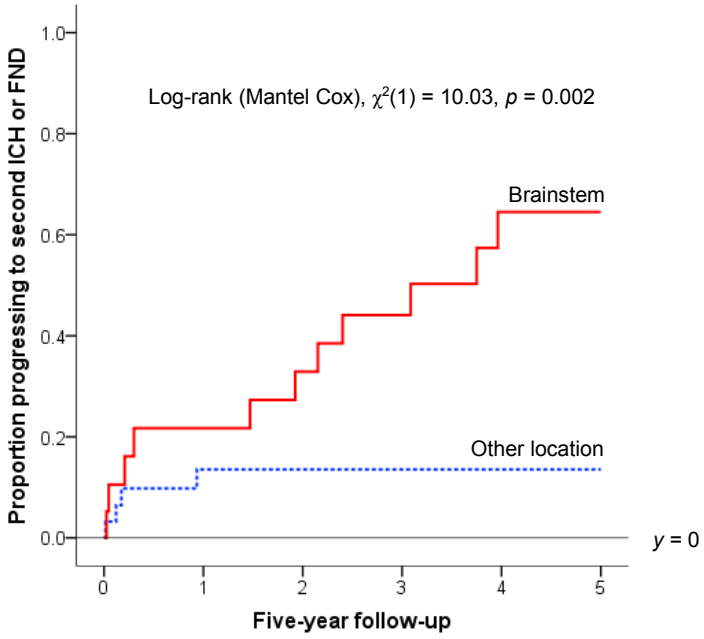
**(A)**




**Number of adults at risk (number of ICH or FND in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Brainstem** | 14 | 11(3) | 8(3) | 7(1) | 6(1) | 6(0) |
| **Other location** | 34 | 22(5) | 19(1) | 16(2) | 16(0) | 14(1) |

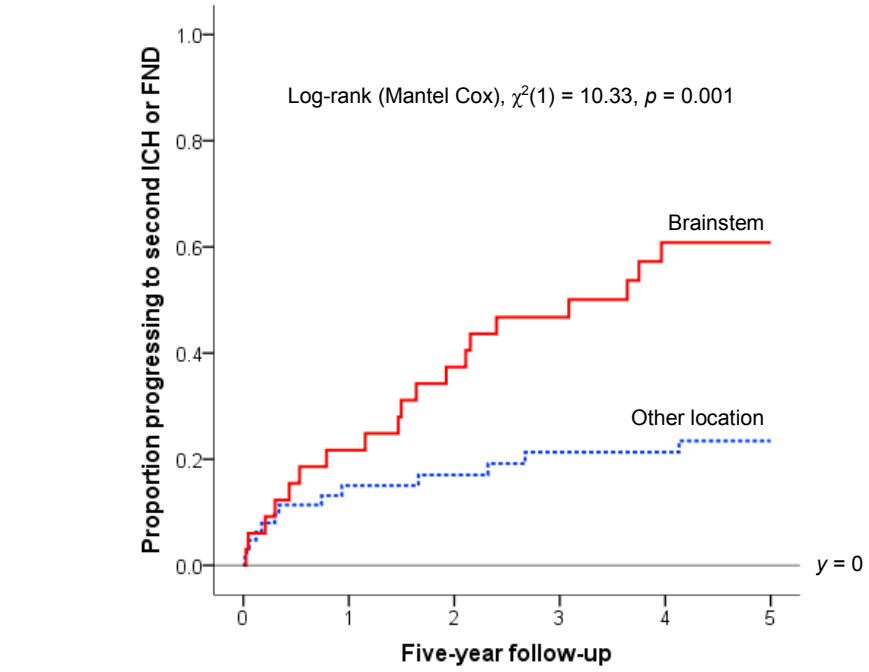
**(B)**




**Number of adults at risk (number of ICH or FND in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Brainstem** | 19 | 14(4) | 12(2) | 9(2) | 4(3) | 2(0) |
| **Other location** | 31 | 23(4) | 22(0) | 21(0) | 21(0) | 15(0) |

**Figure 4.15 Kaplan-Meier plots showing estimated progression to second ICH or FND, stratified by CCM location: (A) 1999–2003 cohort and (B) 2006–2010 cohort**




| Number of adults at risk (number of ICH or FND in preceding year) | | | | | | |
|---|---|---|---|---|---|---|
| **Brainstem** | 33 | 25(7) | 20(5) | 16(3) | 10(4) | 8(0) |
| **Other location** | 65 | 45(9) | 41(1) | 37(2) | 37(0) | 29(1) |

**Figure 4.16 Kaplan-Meier plot showing estimated progression to second ICH or FND, stratified by CCM location: both cohorts**

## Sex and CCM location

In this subsection, the composition of the two cohorts in terms of the two putative predictors is explored, with a view to examining the potential for confounding. In Table 4.12, each cohort is split into two groups – those who experienced a recurrence and those who did not – and the percentage of each sex and CCM location is given for these two groups, and for the entire cohort in the final two rows. In both cohorts, about 40% of those who suffer a recurrence are female with a brainstem lesion; this group comprises 25% of the earlier cohort and 18% of the later cohort.

**Table 4.12 Cohort composition: two putative predictors, stratified by outcome event**

| Description | 1999–2003 cohort | | 2006–2010 cohort | | Pooled cohorts | |
|---|---|---|---|---|---|---|
| | Brainstem | Other | Brainstem | Other | Brainstem | Other |
| **Recurrence** | | | | | | |
| **Female** | 41 | 53 | 40 | 7 | 41 | 31 |
| **Male** | 6 | 0 | 33 | 20 | 19 | 9 |
| **No recurrence** | | | | | | |
| **Female** | 16 | 36 | 9 | 40 | 12 | 38 |
| **Male** | 3 | 45 | 14 | 37 | 9 | 41 |
| **Total cohort** | | | | | | |
| **Female** | 25 | 42 | 18 | 30 | 21 | 36 |
| **Male** | 4 | 29 | 20 | 32 | 12 | 31 |

All figures in this table are percentages.

The percentage of brainstem lesions among those who do not suffer a recurrence is similar (19% and 23%). However, the sex distribution in this subgroup differs among the two cohorts: 16% women and 3% men have brainstem lesions, but suffer no recurrent event within five years in the earlier cohort, compared with 9% women and 14% men in the later cohort.

In Table 4.13, the composition of each cohort and the pooled cohorts is examined with respect to the two putative predictors. For example, men with non-brainstem lesions form 29% of the earlier cohort and 32% of the later cohort: no men in this subgroup suffer a recurrence in the earlier cohort, whereas three men (i.e. 19% of the male, non-brainstem group) have recurrences in the second. In both cohorts, 50% of men with brainstem lesions suffer a recurrence (one in the 1999–2003 cohort, and five in the 2006–2010 cohort), and 58% of women with brainstem lesions in the earlier cohort and 67% in the later have a recurrence. However, in the first cohort, nine women with a non-brainstem lesion (45%) experience a recurrence, in comparison with one woman (7%) in the later cohort.

**Table 4.13 Cohorts, stratified by putative predictors**

| Characteristic | Earlier cohort | | | | Later cohort | | | | Pooled cohorts | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number | | Events | | Number | | Events | | Number | | Events | |
| | *n* | %* | *n* | %† | *n* | %* | *n* | %† | *n* | %* | *n* | %† |
| **Female, brainstem CCM** | 12 | 25% | 7 | 58% | 9 | 18% | 6 | 67% | 21 | 21% | 13 | 62% |
| **Male, brainstem CCM** | 2 | 4% | 1 | 50% | 10 | 20% | 5 | 50% | 12 | 12% | 6 | 50% |
| **Female, non-brainstem CCM** | 20 | 42% | 9 | 45% | 15 | 30% | 1 | 7% | 35 | 36% | 10 | 29% |
| **Male, non-brainstem CCM** | 14 | 29% | 0 | 0% | 16 | 32% | 3 | 19% | 30 | 31% | 3 | 10% |
| **Total** | 48 | 100% | 17 | 35% | 50 | 100% | 15 | 30% | 98 | 100% | 32 | 33% |

**Notes**
*Percentage of total cohort.
†Percentage of characteristic that has a clinical event within five years of presentation: i.e. 58% of women with a brainstem lesion in the earlier cohort suffered a recurrent clinical event within five years of presentation.

### 4.3.5 Functional outcome at the end of follow-up

In this subsection, the level of dependence of adults who have experienced at least one intracranial haemorrhage or focal neurological deficit, definitely or probably due to CCM, is examined. The functional outcome of those who have experienced a single event is compared with those who have suffered at least two events, and the baseline characteristics for adults in both groups in each cohort are displayed in Table 4.14.

Again, the adults in the first cohort are about seven years younger, but there is no age difference between the groups within the cohorts. About a fifth of adults who experienced a single event harbour brainstem lesions, but 47% of adults who suffered a second event in the earlier cohort have a brainstem CCM, compared with 73% in the later cohort. About 80% of adults in all groups have a solitary lesion. Approximately equal numbers of each sex experienced a single event; however, in the earlier cohort 94% of adults who suffered a second event were women, but this decreased to 47% in the later cohort.

**Table 4.14 Comparison of baseline characteristics among adults who experience at least one clinical event in follow-up, stratified by cohort and single or recurrent event**

| | Scotland, 1999–2003 | | | | Scotland, 2006–2010 | | | |
|---|---|---|---|---|---|---|---|---|
| | Single event | | Recurrence | | Single event | | Recurrence | |
| | *n* = 30 | % | *n* = 17 | % | *n* = 35 | % | *n* = 15 | % |
| **Age in years (median, IQR)** | 39 | 30–56 | 38 | 31–54 | 46 | 32–61 | 46 | 33–58 |
| **Male** | 14 | 47% | 1 | 6% | 18 | 51% | 8 | 53% |
| **Female** | 16 | 53% | 16 | 94% | 17 | 49% | 7 | 47% |
| **Brainstem CCM** | 6 | 20% | 8 | 47% | 8 | 23% | 11 | 73% |
| **Other location** | 24 | 80% | 9 | 53% | 27 | 77% | 4 | 27% |
| **Single CCM** | 24 | 80% | 14 | 82% | 27 | 77% | 12 | 80% |
| **Multiple CCM** | 6 | 20% | 3 | 18% | 8 | 23% | 3 | 20% |

As described in subsection 4.2.2 above, at the time of presentation, each participant's functional outcome is assessed, using the Oxford Handicap Scale, and then, in subsequent years at around the anniversary of CCM diagnosis, SIVMS contacts each participant's general practitioner to request a new OHS rating. In the first cohort, of the 47 adults alive after a first clinical event, nine were censored in the first two years of follow-up, after interventional treatment (seven in the single-event group and two in the recurrence group); another two (both in the recurrence group) were censored at treatment later in follow-up, and four people in this cohort died, one death of which was attributable to CCM.

In the second cohort ($n = 50$), ten participants were censored for treatment – six in the single-event group and four in the second – and a further two were censored for treatment in later years (one in each group). Two adults died during the first two years. In addition, 13 adults did not have OHS scores for all five years of follow-up, since their initial presentation was after June 2008.

In Figures 4.17–4.20, OHS scores for presentation and the five years of follow-up are displayed as stacked bar charts for each cohort, stratified by clinical-event group, which is determined by whether the participant has experienced a single or a second event. Figures 4.17–4.18 refer to adults in the earlier cohort and Figures 4.19–4.20 to adults in the later cohort. In Figures 4.17 and 4.19, participants are censored at the time of interventional treatment, and therefore the populations included in these figures are identical to those in the analyses in subsection 4.3.3. Figures 4.18 and 4.20 act as sensitivity analyses and include all adults – irrespective of whether or not they have received interventional treatment. Completeness of follow-up was quantified by expressing total follow-up obtained as a percentage of the total follow-up that could potentially have accrued (Clark et al., 2002). Thus completeness for OHS scores at presentation and the first five years was 89.7% in the earlier cohort and 84.3% in the later cohort, after adjustment for the years in the latter cohort when follow-up was not possible.

OHS scores 0–1 (shown in blue) represent favourable outcome (no or minor symptoms with no interference to lifestyle), and OHS 2–5 (the orange bars) represent unfavourable outcome, ranging from a minor to severe handicap.

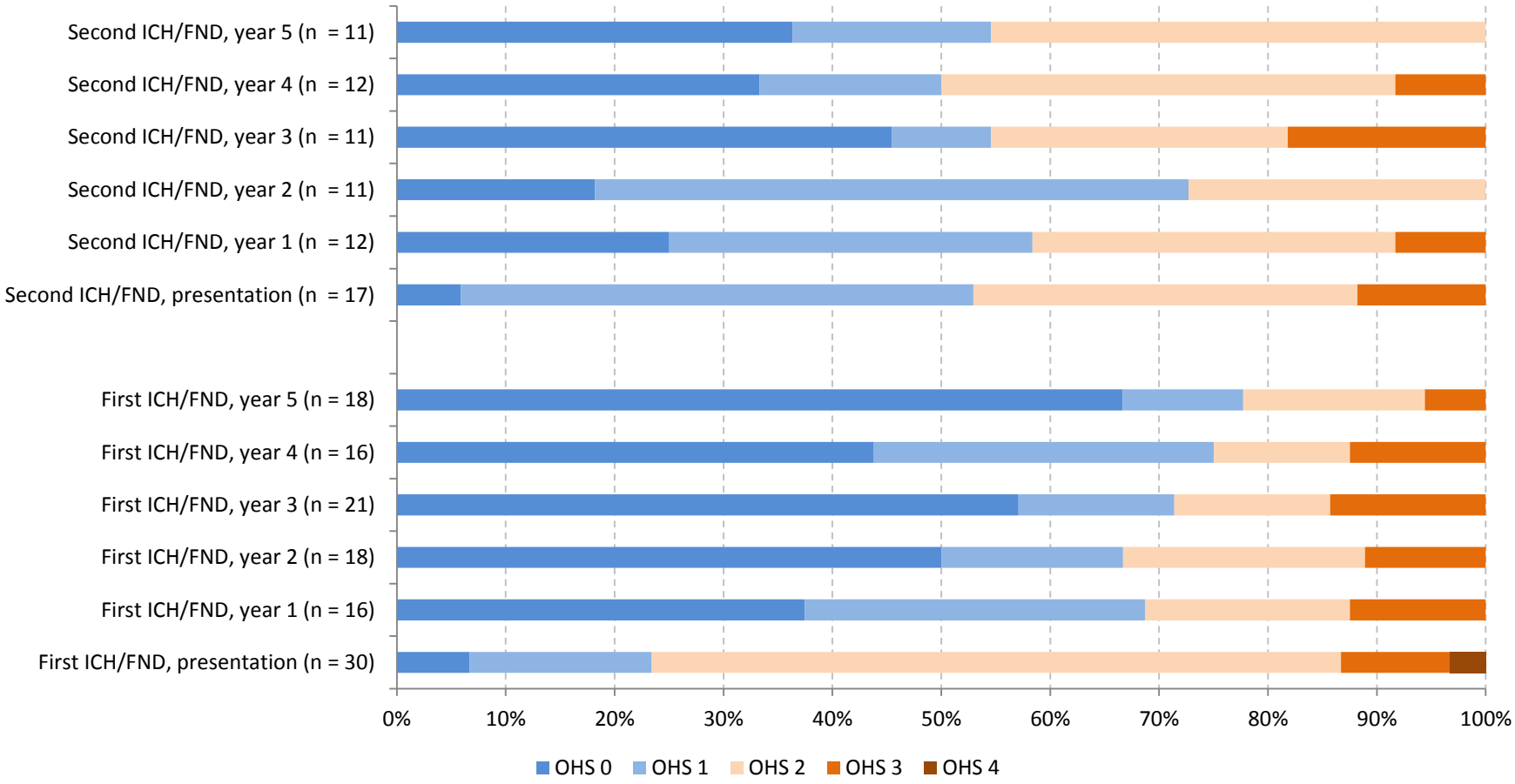



**Figure 4.17 Dependence measured on the Oxford Handicap Scale for survivors of first and second intracranial haemorrhage or focal neurological deficit in SIVMS, 1999–2003 (adults censored at time of interventional treatment)**

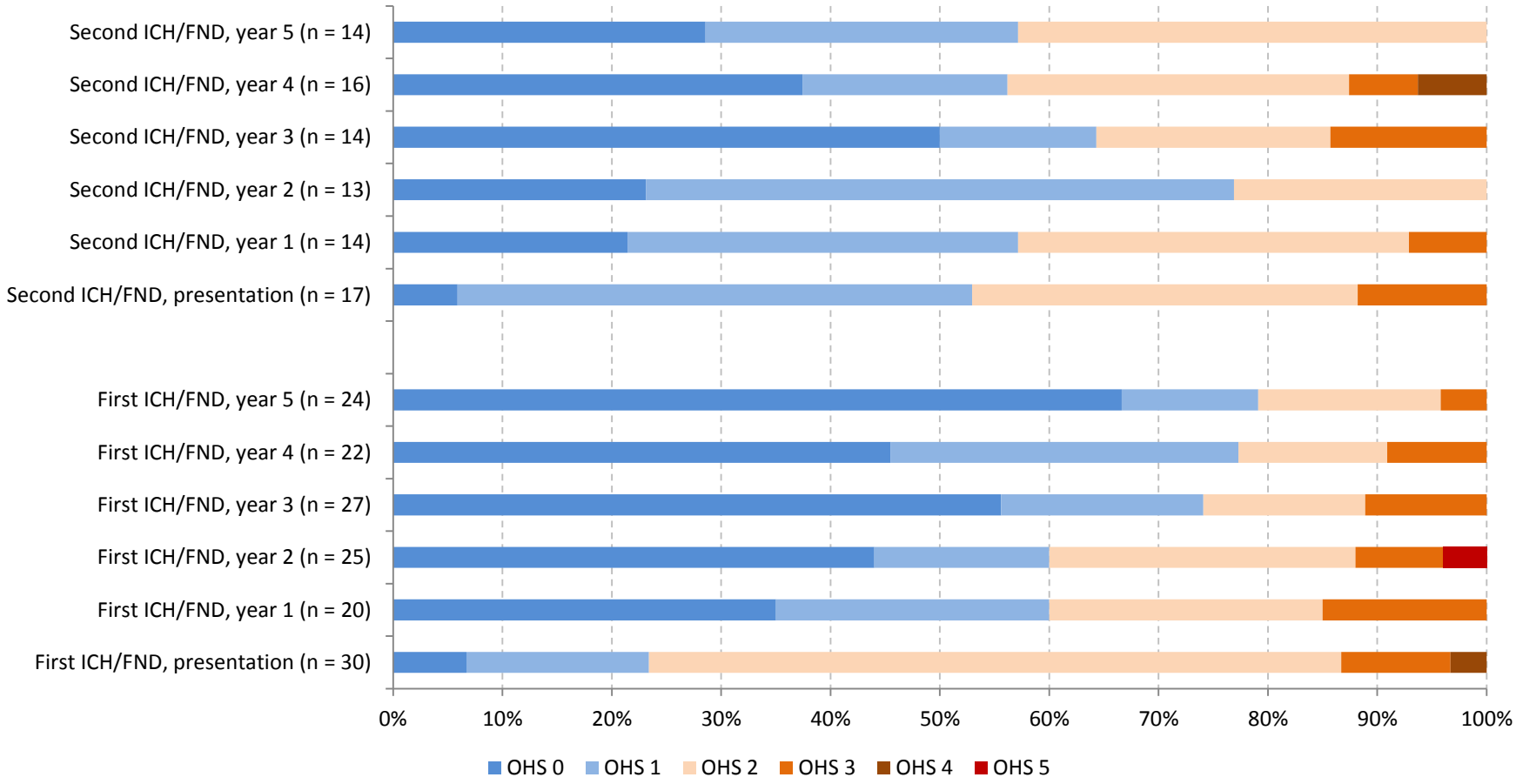



**Figure 4.18 Dependence measured on the Oxford Handicap Scale for survivors of first and second intracranial haemorrhage or focal neurological deficit in SIVMS, 1999–2003 (including adults who have undergone interventional treatment)**

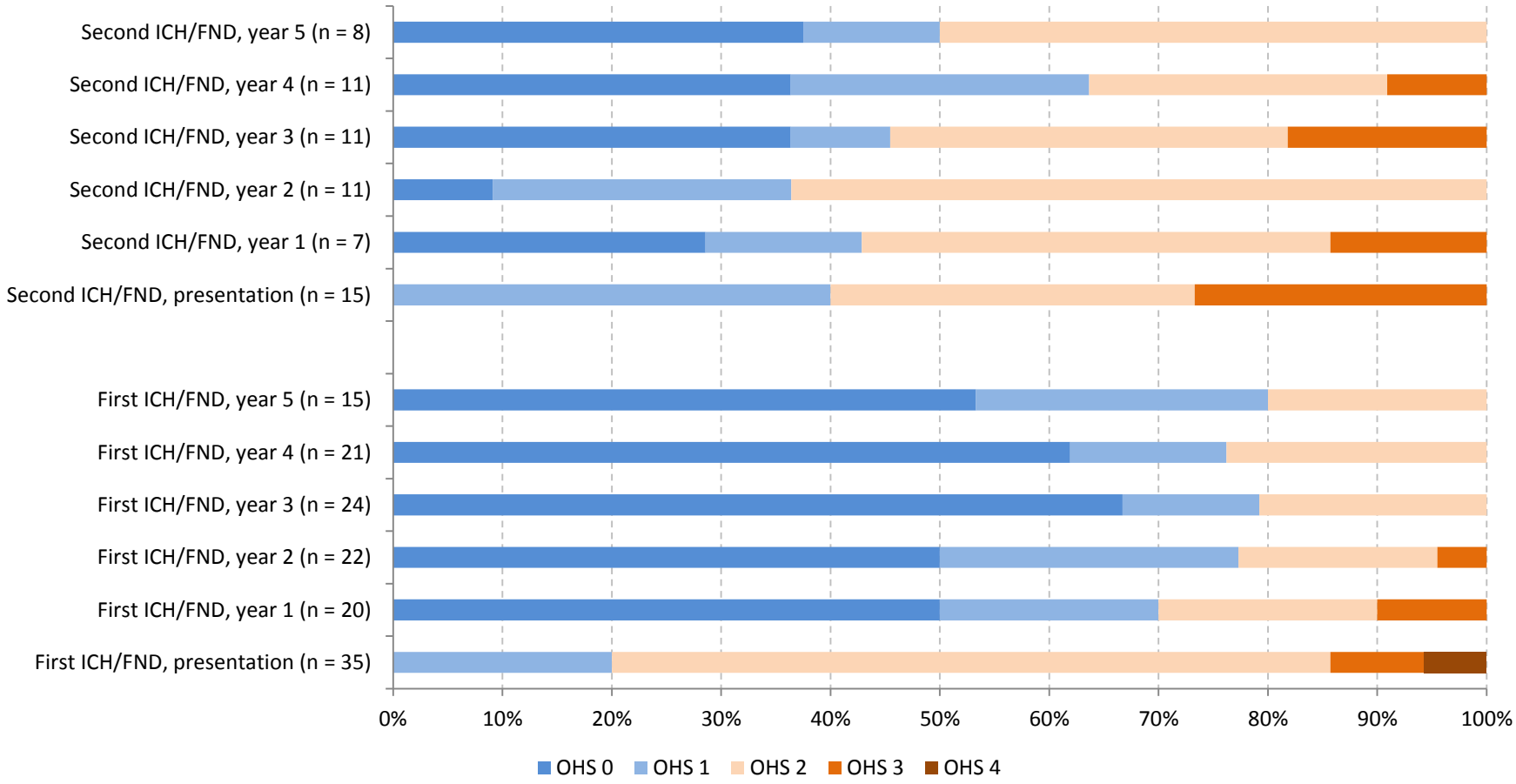



**Figure 4.19 Dependence measured on the Oxford Handicap Scale for survivors of first and second intracranial haemorrhage or focal neurological deficit in SIVMS, 2006–2010 (adults censored at time of interventional treatment)**

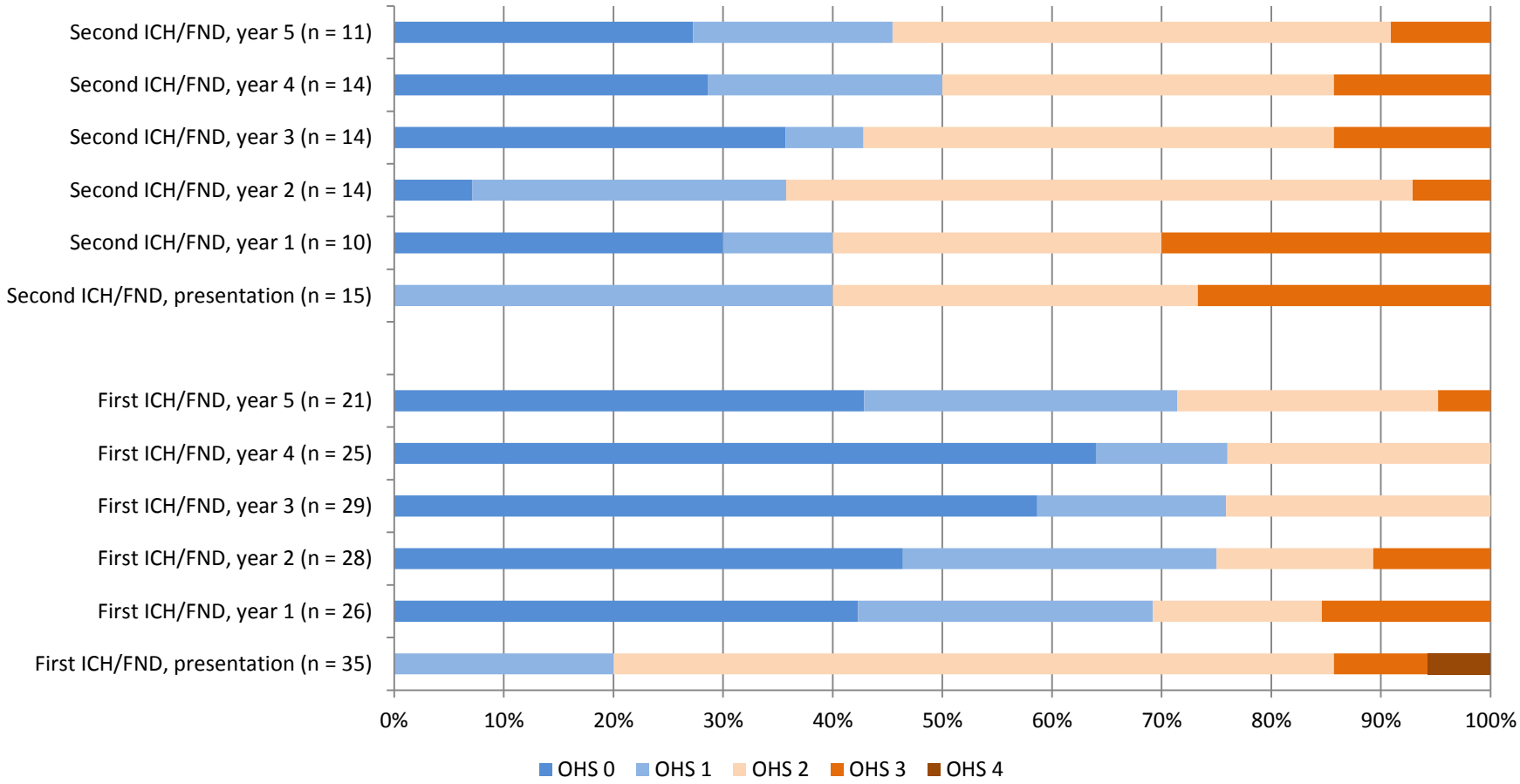



**Figure 4.20 Dependence measured on the Oxford Handicap Scale for survivors of first and second intracranial haemorrhage or focal neurological deficit in SIVMS, 2006–2010 (including adults who have undergone interventional treatment)**

Three adults in the earlier cohort were rated OHS 0 at presentation. In both cohorts, counterintuitively, those who did not have a subsequent event tended to have a worse OHS rating at presentation than those who suffered another clinical event during follow-up (about 20% in the single-event groups are rated OHS 0–1 compared with 53% [earlier cohort] and 40% [later cohort] in the recurrent group). The worst grade for either cohort at presentation is OHS 4, occurring in both single-event groups and OHS 3 for those who suffered a second event.

During follow-up, OHS scores among those censored at the time of interventional treatment range from 0 to 3 in both cohorts, although in several years the lowest score is OHS 2. When those who received interventional treatment are included, one adult in the single-event group of the first cohort was rated OHS 5 in year 2 (in 2003, the year after treatment; between 2008 and 2013, however, he alternated between OHS 0 and 1), and a woman in the recurrence group of the same cohort was rated OHS 4 in year 4 (in 2005; again, her level of dependence improved subsequently, and since 2008 she has been rated OHS 2, whenever a rating has been received).

The distribution of OHS scores for those who experience a single event is similar in both cohorts: over the five years of untreated follow-up, the percentage who are rated OHS 0–1 ranges from about 70% (in the first year after presentation) to about 80% (after five years). The number of adults who suffered a second event and received an OHS score during untreated follow-up is small in both cohorts (between seven and twelve), so percentages are rather unreliable. In the first cohort, 50–60% are rated OHS 0–1 each year, with the exception of year 2, where 73% are rated as having a favourable outcome. In the later cohort, 36–50% are rated OHS 0–1 in four years; four years after the first event 64% are rated as having a favourable outcome.

In summary, of those adults whose level of dependence was graded during follow-up in either cohort, about two-thirds of all survivors of an intracranial haemorrhage or focal neurological deficit (63–72%) have a favourable outcome, with no interference to lifestyle; about a quarter (19–30%) have some restrictions to lifestyle, but are able to look after themselves (OHS 2), and 3–16% have a moderate handicap, with significant restriction to lifestyle (OHS 3).

## 4.4 Discussion

*Study design*

The Scottish Intracranial Vascular Malformation Study (SIVMS) was meticulously designed to minimize potential sources of bias (Al-Shahi et al., 2003a, Al-Shahi et al., 2003b, Al-Shahi Salman, 2005). By adopting a prospective, population-based design, recall and selection biases were minimized: recall bias is a problem in retrospective studies, and hospital-based studies tend to include the more seriously ill patients, whereas those patients whose lesions only have very mild side-effects and are treated by primary-care providers, and also those individuals in the community who die suddenly as a result of a haemorrhage tend to be missed. A clear inception point of symptom onset leading to a first-ever CCM diagnosis was adopted. Multiple overlapping sources of case ascertainment were used to identify adults with cerebral cavernous malformations, and two neuro-radiologists independently reviewed the original diagnostic imaging to confirm CCM diagnosis; strict diagnostic criteria and outcome definitions were applied to avoid detection and misclassification biases; neuro-imaging, pathology reports and case notes were reviewed to determine mode of initial clinical presentation; multiple overlapping sources of follow-up were – and continue to be – used to avoid information bias; assessors used all the clinical, radiological and pathological information available and were masked to potential prognostic features (sex and CCM location) to prevent bias in outcome assessment. Nevertheless, it is possible that the number of haemorrhages that occurred over the five-year period was underestimated, since haemorrhages can occur with a seizure and not every adult who suffers a seizure is referred for neuro-imaging.

*Composition of cohorts*

The composition of the second cohort is slightly older across all presentation types, but this is unlikely to be accounted for by the fact that no recruitment occurred during the years 2004 and 2005. Although a seemingly plausible explanation for the increased

age of the second cohort might be that some adults who would have been diagnosed in these two years were diagnosed a few years later, this does not appear to be borne out by the recruitment pattern in the second cohort. When year of diagnosis in the second cohort is examined, the least number of adults were diagnosed in 2006, and the largest numbers in the final two years (37 and 40 respectively).

Examining the composition of both cohorts, those presenting incidentally and with FNDs tend to be older. This may be consistent with the theory that it is more common to investigate possible haemorrhagic symptoms in young, normotensive adults (Josephson and Al-Shahi Salman, 2011). This suggestion is further supported by the fact that there are fewer adults recorded with an FND presentation in the second cohort (6% compared with 15%), and those who are recorded have a median age of 57 years (IQR 52–60), compared with a median age of 40 years (IQR 32–59) in the first cohort.

It is conceivable that general practitioners increased the number of patients they referred for neuro-imaging over the course of the two recruitment periods; this might account also for the increase in the percentage of adults presenting with seizure and ICH in the later cohort. It is also plausible that, over the course of the two recruitment periods, clinicians may have begun to refer slightly older patients with haemorrhagic symptoms for neuro-imaging; this might account for the older age-group presenting with FND in the second cohort, since some of those with FND presentation in the first cohort might in fact have been haemorrhagic presentation, had the appropriate neuro-imaging been performed at the appropriate time. It is also possible, however, that MRI has become more sensitive over the study period and it has therefore become easier for neuro-radiologists to detect blood on the imaging in the later period.

These two cohorts were drawn from the same population at different time periods, but were analysed separately, both in this and later chapters. This decision was taken for three reasons. First, separate analyses enabled a comparison of the number of outcome events that occurred over the two time-periods, at what stage in the follow-up period they occurred, and the consequent estimated risks of each event, since recruitment in the first cohort was between 1999 and 2003, and in the second between 2006 and 2010. It was not known whether MRI sensitivity had increased sufficiently during this period

to have had an effect on the number of clinical events detected. Second, the data pertaining to the earlier cohort were analysed in 2011, before any follow-up could be accrued for the final year of recruitment in the later cohort. Finally, the first cohort had a minimum of nine years follow-up (although this was truncated to five years in the analyses), whereas not every member of the second cohort was able to contribute the full five years of follow-up, because recruitment ended on 31 December 2010.

*Haemorrhage and focal neurological deficit in follow-up*

The estimated five-year risk of a recurrent intracranial haemorrhage definitely attributable to CCM was significantly greater than the similar risk for a first haemorrhage, in both cohorts. However, it should be borne in mind that the number of haemorrhages in the five-year follow-up period was very small: two (one) ICH among those who presented incidentally or with a seizure in the first (second) cohort, and six (nine) ICH among those who presented with a haemorrhage or had experienced one earlier in follow-up in the first (second) cohort.

Furthermore, most haemorrhages occurred within the first eighteen months of follow-up, and the estimated annual risk appeared to decrease over the course of the five years. In a similar manner, the estimated risk of a second clinical event due or possibly due to CCM was significantly greater than the risk of a first event, and again the annual risk diminished over time.

The long-term risk of an ICH/FND in untreated follow-up remains uncertain: in the first cohort, a single participant experienced a clinical event in untreated follow-up more than five years after initial presentation (two non-haemorrhagic FNDs possibly due to CCM, 11.5 and 12.7 years after presentation). Therefore it would appear that the data from the earlier Scottish cohort support Barker and colleagues' hypothesis that clinical events tend to cluster in time for a period of two or three years, and then the risk reverts to baseline (Barker II et al., 2001).

*Sex as a predictor in the earlier cohort*

Another difference between the two cohorts is the percentage of women who presented with ICH or FND: 71% in the first cohort and 51% in the second. The data in the first cohort were analysed more than two years before the data in the second cohort, and therefore for this intervening period it seemed very probable that sex was a predictor of a recurrent clinical event in follow-up: sixteen women and a single man from the first cohort experienced a recurrent event, and women had an increased risk of a second event (log-rank $\chi^2(1) = 6.21$, $p = 0.013$) (see Figure 4.13(A)). In addition, biological mechanisms appeared to support this result, as it has been proposed previously that a CCM might respond to an increase in hormones during pregnancy, contraception or hormone replacement therapy (Robinson et al., 1991, Aiba et al., 1995, Abdulrauf et al., 1999, Moriarity et al., 1999, Wang et al., 2003, Pozzati et al., 1996). When the second cohort were analysed, however, the progression to second event was similar for both sexes, and indeed for the first four years, men appeared to have a slightly increased risk of a second event (Figure 4.13(B)).

The medical records of the women in the earlier cohort who had experienced at least one clinical event were examined in greater depth, in an attempt to investigate whether oral contraception, pregnancy or hormone replacement therapy might have played a part in this increased risk. Nothing conclusive could be discovered, partly because the number of women who had experienced at least one clinical event was small ($n = 32$), and the women ranged in age from 23 years at presentation to 82 (median 39 years, interquartile range 33–58 years). With hindsight, it would appear that the fact that almost everyone who had a recurrence in the first cohort was female was an example of this cohort being located in the extreme tail of a theoretical sampling distribution, and the hypothesized increased risk among women was a statistical artefact.

*Dependency*

The functional outcome for participants in both cohorts with a single event was high over the first five years of follow-up, with over two-thirds being rated OHS 0–1. Among those who experienced at least two events within five years, 50–60% in the first cohort and 40–50% in the second cohort were rated OHS 0–1.

However, this dichotomization into favourable versus unfavourable outcome is sometimes split so that favourable outcome includes OHS 2 (minor handicap: some restrictions, but able to look after self) (Bamford and Sandercock, 1989). If this dichotomization – OHS 0–2 versus OHS 3–5 – is used, then in most years at least 85% of adults, and in some years 100%, achieved a favourable outcome. This illustrates that, in general, the level of morbidity associated with cerebral cavernous malformation is low; none the less, it must be borne in mind that for a few less fortunate individuals, this is not the case and they experience OHS levels of 4 or 5.

Functional outcome is a valuable measure for clinicians to employ when describing to newly diagnosed adults the untreated course of the condition. Five years after diagnosis, over 50% of adults who survived two clinical events had a favourable outcome (OHS 0–1) (and this extends to 100%, if favourable outcome is broadened to include OHS 2).

*Concluding comment*

Fortunately, comparatively few members of either cohort suffered a clinical event within five years of untreated follow-up. However, from a statistical point of view, the infrequency of outcome events created problems for modelling the untreated course of the disease, and it was impossible to build a prognostic model using the data from the first cohort alone. Thus several other research groups were invited to collaborate, so that an individual patient data meta-analysis could be undertaken; this is described in Chapters 6–9 below.

# Chapter 5: Comparison of outcome among treated and conservatively managed adults in the first Scottish cohort

## 5.1 Introduction

As was discussed in Chapter 2, with the increased availability and usage of magnetic resonance imaging (MRI) over the past 25 years, and with more sophisticated neuro-imaging techniques continually being developed, more people have received a first-ever diagnosis of cerebral cavernous malformation. In particular, during this period an increasing number of people who are asymptomatic have been diagnosed incidentally; for example, of the 141 adults resident in Scotland who received a first definite CCM diagnosis between 1999 and 2003, 67 (48%) were diagnosed incidentally.

As a result of this increase in diagnosis, clinicians frequently encounter a dilemma of how best to treat patients with CCM: whether to advise surgery to remove the lesion, on the one hand, with the attendant risks of morbidity and death; or whether to advocate conservative management, and thereby expose the patient to a lifetime risk of haemorrhage or focal neurological deficit. This situation is particularly challenging in the case of adults with hitherto asymptomatic lesions. To date, very few comparative studies have been undertaken that investigate the outcome of those who undergo interventional treatment for their cavernous malformations and those who are conservatively managed.

For an individual with a non-haemorrhagic presentation who has not undergone any interventional treatment, the five-year risk of a first ICH due to CCM is estimated to

be 2.4% (95% CI 0% to 5.7%), and the five-year estimated risk of a recurrence is 29.5% (95% CI 4.1% to 55.0%) (see Chapter 4 above) (Al-Shahi Salman et al., 2012). Moreover, as was observed in Chapter 4, the risk of a recurrent haemorrhage appears to decrease within five years of the initial haemorrhage (Barker II et al., 2001, Al-Shahi Salman et al., 2012, Flemming et al., 2012). In addition, the volume of an intracranial haemorrhage due to a cavernous malformation tends to be small (average volume is approximately 1.8 $cm^3$), due to CCM angioarchitecture, and functional outcome after the haemorrhage tends to be good (Cordonnier et al., 2008, Moultrie et al., 2014).

In this chapter, after a brief synopsis of the available research, the functional outcome of all adults in Scotland who received a cavernous malformation diagnosis between 1999 and 2003 is examined.

## 5.2 Recent research

There have been very few published studies comparing outcome after CCM excision with conservative management. Most studies that do exist tend to have one or more flaws: small sample size, short follow-up periods, a highly-selected patient base (for example, patients with brainstem CCM or CCM in eloquent areas of the brain) (Tarnaris et al., 2008, Huang et al., 2010, Menon et al., 2011, Wostrack et al., 2012).

In a recent review of the literature concerning intractable epilepsy among patients diagnosed with CCM, the authors concluded ‘a large proportion of recent studies on surgery for CCM-associated epilepsy are not using criteria and definitions for the classification of epilepsy and outcome that are commonly used by epileptologists or epilepsy surgeons. This results in limited usefulness of a large part of the literature’ (von der Brelie and Schramm, 2011). Furthermore, several studies were published over fifteen years ago; neuro-imaging, neuro-navigation, electrophysiological monitoring, and microsurgical and radiosurgical techniques have all improved in the ensuing

period, and therefore a comparison of conservative and surgical management of CCM that was undertaken more than fifteen years ago is of limited relevance.

Recinos et al. published a summary of advantages and disadvantages of conservative and surgical treatment, according to type of presentation and CCM location (Recinos et al., 2011). In a recent systematic review of comparative studies (Poorthuis et al., 2013), Poorthuis and colleagues found sixteen observational studies comparing either surgical excision or stereotactic radiosurgery with conservative management: five studies investigated adults with a CCM who had experienced a prior haemorrhage, and eleven investigated patients with a CCM who suffered epileptic seizures. Of these sixteen studies, only two in the latter group demonstrated a 'dramatic effect' (i.e. less than 1% probability that both groups of observations came from the same population, and a rate ratio greater than 10) (Glasziou et al., 2007), and these latter two were considered to be at high risk of bias (Poorthuis et al., 2013). The authors concluded that 'there is a need for large studies of CCM treatment with a concurrent control group, ideally with randomized treatment allocation' (Poorthuis et al., 2013).

In a systematic review and meta-regression analysis on CCM interventional treatment, Poorthuis and colleagues identified 63 cohorts, 49 of which reported on neurosurgery (2,684 patients with 6,707 patient-years of follow-up) and 14 on stereotactic radiosurgery (740 patients with 3,322 patient-years of follow-up), eleven using Gamma Knife and three using a linear accelerator (Poorthuis et al., 2014). However, the length of follow-up for these studies was comparatively short (median length 2.3 years, 95% CI 0.1 to 8.1 years), and only three of the 63 studies fulfilled the researchers' criteria for being classified as 'high-quality' studies, which was too few to conduct their planned sensitivity analysis. They concluded that:

> 'The reported risks of CCM treatment (and the lower risks of neurosurgical excision over time, from recently bled CCMs, and for CCMs outside the brainstem) compare favourably with the risks of recurrent haemorrhage from CCM. Long-term effects, especially important for stereotactic radiosurgery, are unknown.' (Poorthuis et al., 2014)

## 5.3 Methods

### 5.3.1 Research aim

The primary aim of this chapter is to answer the following research question: how does the functional outcome of adults diagnosed with CCM who have undergone interventional treatment compare with those who have been managed conservatively over the course of a five-year follow-up period? It should be emphasized that no prior hypothesis was formulated at the beginning of this study as to whether interventional treatment would improve or worsen the functional outcome of adults diagnosed with CCM.

### 5.3.2 Study design

This is a comparative study, nested in a prospective, population-based observational cohort study of the management of adults with cavernous malformations. The adults who received CCM excision (cases) and the adults who were conservatively managed (controls) were concurrent.

### 5.3.3 Participants

All adults in the first cohort of the Scottish Intracranial Vascular Malformation Study (presenting between 1999 and 2003) who had received a definite CCM diagnosis and who were alive at presentation were included in this analysis. The period at risk was dichotomized into treated and untreated follow-up. Patients were classified as being managed conservatively, if they had not received interventional treatment for their cavernous malformation within five years of initial presentation, or as treated, if they had undergone surgical intervention or stereotactic radiosurgery within five years of initial presentation. It was necessary to specify a time window in which treatment had

occurred to ensure that there was a sufficient period of time for follow-up after treatment. Treatment strategy was decided by local clinicians.

### 5.3.4 Inception and follow-up

Methods of case ascertainment, follow-up, and definitions of ICH and FND have been described in Chapter 4 above. The inception point for the conservatively managed group was the date of initial presentation, which was the date of symptom onset – or the date of medical presentation, if the patient was asymptomatic – that directly led to a diagnosis of cavernous malformation. For the treated group, inception was the date of first intervention within five years of initial presentation.

As described in Chapter 4, each year, on the anniversary of the date of diagnosis, a postal questionnaire is sent to every general practitioner, seeking an assessment of the patient's functional outcome, using the Oxford Handicap Scale (OHS), which is derived from the modified Rankin scale. The Oxford Handicap Scale ranges from 0 ('no handicap: no change to lifestyle') to 5 ('severe handicap: totally dependent; requires constant attention day and night') and 6 (death) (Bamford and Sandercock, 1989) (see Table 5.1).

### 5.3.5 Statistical analysis

#### Baseline characteristics

As in Chapter 4, in the descriptive analysis, mode of initial clinical presentation was categorized into four groups: ICH, FND, seizure or incidental; and CCM location was categorized as brainstem (in the midbrain, pons or medulla), cerebellar, deep (in the thalamus, basal ganglia or choroidal), or lobar (all other locations). However, in the univariate and multivariable analyses, mode of clinical presentation was dichotomized as ICH or FND at presentation versus incidental or seizure at presentation, and location

**Table 5.1 The Oxford Handicap Scale**

| Handicap | Lifestyle | Grade |
|---|---|---|
| None | No change | 0 |
| Minor symptoms | No interference | 1 |
| Minor handicap | Some restrictions, but able to look after self | 2 |
| Moderate handicap | Significant restriction; unable to lead a totally independent existence (requires some assistance) | 3 |
| Moderate-to-severe handicap | Unable to live independently, but does not require constant attention | 4 |
| Severe handicap | Totally dependent; requires constant attention day and night | 5 |
| Dead | Dead | 6 |

**Reference:** (Bamford and Sandercock, 1989).

as brainstem versus all other locations. CCM multiplicity was grouped as single versus multiple. When comparing baseline characteristics between treatment groups, parametric methods of analysis were used where data were normally distributed, and non-parametric methods where they were not; odds ratios (together with 95% confidence intervals) were used to compare categorical variables; and exact tests where cell counts were less than five.

## Follow-up

Treated follow-up was defined as all available follow-up from the date of a first intervention (that occurred within the first five years of follow-up), until the first outcome event or censoring. Untreated follow-up was divided into two groups: (i) all available follow-up from inception date until the first outcome event or censoring at five years for those adults who did not have an intervention within five years of presentation; or (ii) all available follow-up from inception until the date of a first intervention that occurred within five years of first presentation. Censoring occurred at the earliest occurrence of death unrelated to CCM, last available follow-up or five years after the start of follow-up.

The untreated clinical course in the treated group was described – that is, the number of people who experienced a clinical event, whether due to the CCM or unknown cause, between presentation and intervention dates – but not included in the statistical analysis. If a participant had either an intracranial haemorrhage or new focal neurological deficit, due or possibly due to CCM, in this untreated period, then the dataset was adjusted so that the individual 'presented' with the last event before intervention (thus the primary mode of clinical presentation, age at presentation and possibly the CCM location could be changed). Deaths and their causes that occurred within 30 days of treatment were also described.

*Primary outcome*

The primary outcome of this analysis was 'sustained poor outcome', which was defined as two successive OHS scores ≥ 2, occurring within five years of the start of follow-up (after presentation date for the conservatively managed group and after intervention date for the treated group) (see Table 5.2 for a demonstration of the method used to calculate sustained poor outcome). An OHS score of 2–6 was determined as 'poor outcome', since OHS 2 is defined as 'minor handicap: some restrictions, but able to look after self' and, in general, cavernous malformations tend to have low morbidity. If a participant's OHS scores were missing for the next one or two years after a first score of OHS 2–5, but the first available score was also OHS 2–6, then this outcome was included in the definition of sustained poor outcome (see Table 5.2). Both OHS scores that contributed to the outcome measure occurred during the follow-up period, or the sixth year after inception; that is, the initial, baseline OHS score was not used to determine the primary outcome.

The annual functional outcome for the treated group was adjusted to ensure that the first OHS scores to be used for this group occurred between 5 and 18 months after the date of first intervention, and at approximate annual intervals thereafter.

**Table 5.2 Calculation of sustained poor outcome**

| OHS ratings | | | | | | | Comments | |
|---|---|---|---|---|---|---|---|---|
| Presentation | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** | | |
| **0** | 0 | 0 | 3 | 2 | 1 | 1 | Sustained poor outcome occurred:<br>start date for treated group:<br>start date for conservatively managed group: | <br>year 3<br>midway between years 2 and 3 |
| **1** | 2 | 0 | 2 | 1 | 3 | 1 | Sustained poor outcome did **not** occur : | |
| | | | | | | | *No **successive** OHS 2–6 ratings* | |
| **1** | - | 2 | - | - | 2 | 3 | Sustained poor outcome occurred:<br>start date for treated group:<br>start date for conservatively managed group: | <br>year 2<br>midway between presentation and year 2 |
| | | | | | | | *No OHS ratings available in years 3 and 4, so first OHS 2–6 rating in year 2 carries over to second OHS 2–6 rating in year 5* | |
| **1** | 2 | 1 | - | - | 2 | 3 | Sustained poor outcome occurred:<br>start date for treated group:<br>start date for conservatively managed group: | <br>year 5<br>midway between years 2 and 5 |
| | | | | | | | *Year 1 rating followed by OHS 1 in year 2, so year 5 is the first of two successive OHS 2–6 ratings* | |
| **3** | 2 | 1 | - | - | 2 | 3 | Sustained poor outcome occurred:<br>start date for treated group:<br>start date for conservatively managed group: | <br>year 5<br>midway between years 2 and 5 |
| | | | | | | | *Presentation rating not included in sustained poor outcome calculation* | |

For the conservatively managed group, however, unless the participant died within the first year of follow-up, the first possible OHS score was at least one year after the date of presentation, since questionnaires requesting OHS ratings were sent to family doctors annually on the anniversary of the presentation date. To avoid an apparent artificial time-lag between treated and conservatively managed groups, the start date of sustained poor outcome for the untreated group was calculated so that it occurred midway within the observation period (i.e. midway between the last OHS score 0–1 and the first OHS score 2–6) (see Table 5.2), with the rationale that sustained poor outcome is a gradual process rather than a specific event that happens on a particular day.

### *Secondary explanatory outcome*

The secondary – explanatory – outcome was a composite endpoint of symptomatic cerebral infarction, intracranial haemorrhage or new focal neurological deficit (Al-Shahi Salman et al., 2008). Cerebral infarction was defined by clinical signs of focal or global neurological disturbance that developed rapidly and lasted for 24 hours or longer, with the proviso that this diagnosis was supported by appropriate neuro-imaging or pathological examination. These three events were independently classified as definitely attributable to a CCM, possibly attributable to a CCM (due to lack of a more plausible explanation) or attributable to CCM treatment. A sensitivity analysis was undertaken for the secondary outcome: events that were definitely attributable to a CCM or attributable to surgery were included, and events possibly attributable to a CCM were excluded from the analysis.

## Analysis

Kaplan-Meier survival curves (one minus Kaplan-Meier estimate) for the primary and secondary outcomes, each plot stratified by treatment group, were constructed to display the cumulative proportion of each group that experienced the outcome; log-rank tests were used to compare the two curves.

For both primary and secondary outcomes, four predictors of interest among the baseline characteristics were pre-specified in the following order: age at start of follow-up (or treatment); primary mode of clinical presentation; CCM location; and sex. The fifth predictor was treatment group. These variables were selected on account of their clinical relevance; their known or hypothesized relevance in the medical literature; and the accuracy, reliability and completeness of data collection.

Cox proportional hazards regression was used in the univariate analyses for both primary and secondary outcomes, to determine the unadjusted hazard ratios for each potential predictor, if the proportional hazards assumptions were satisfied (Machin et al., 2006). This model is expressed in terms of the hazard function, $h(t)$, which is the instantaneous rate of an event happening at time *t*, given that it has not occurred up to time *t*:

$$h(t) = h_0(t)\exp(b_1 x_1)$$

where $h_0(t)$ is the baseline or underlying hazard function, when the covariate, $x_1$, has the value of 0, and $b_1$ is the regression coefficient; values for $h_0(t)$ and $b_1$ are estimated from the data.

In the multivariable analyses for each outcome, Cox regression was again used and the model took the form

$$h(t) = h_0(t)\exp(b_1 x_1 + b_2 x_2 + \cdots + b_p x_p)$$

where $x_1$ to $x_p$ are the covariates in the model, and $b_1$ to $b_p$ are the regression coefficients, which are all estimated from the data. For both outcome measures, hazard ratios were adjusted by any factors imbalanced at baseline and/or known to influence CCM prognosis. However, because the main objective was to examine the impact of treatment on outcome, rather than to create a model, the rule that the number of predictors entered into the analysis should be governed by the number of outcome events was relaxed (Harrell et al., 1984, Concato et al., 1995, Peduzzi et al., 1995), and all pre-specified covariates were entered into the analyses.

The sample size for this analysis was not pre-specified; however, the aim was to identify every new definite diagnosis of CCM (i.e. validated by MRI or pathological examination) within a five-year period in a single country, and to accumulate at least five years of follow-up for every member of the cohort.

## 5.4 Results

### 5.4.1 Treatment groups

Between 1999 and 2003, 141 adults resident in Scotland received a first-ever definite diagnosis of cerebral cavernous malformation, which was validated by MRI ($n$ = 135) or pathological examination, following surgical excision ($n$ = 1) or autopsy ($n$ = 5) (see Figure 5.1). The five participants who were diagnosed at autopsy were not included in the analysis, since they did not contribute any follow-up. In addition, when the analysis was undertaken (summer 2012), the diagnosis of two adults had not been confirmed as definite; therefore these participants were not included in this analysis. In fact, these two patients were conservatively managed, suffered neither intracranial haemorrhage nor focal neurological deficit in follow-up, and their Oxford Handicap Scale (OHS) scores were unavailable until the year 2009/2011 (which was more than five years after presentation); since then one has a consistent score of 0, and the other scored a single 2 and has since alternated between 0 and 1.

During the first five years of follow-up, 25 adults (19%) underwent microsurgical CCM treatment, no one received stereotactic radiosurgery, and 109 adults (81%) were conservatively managed. Two adults underwent surgery more than five years after presentation; they are included in the conservatively managed group as they each had five years of untreated follow-up. Although a potential five-year period between presentation and intervention had been specified, all 25 adults in the treated group had surgery within three years of presentation. The median time between presentation and intervention was 10 months (IQR 4.7–16.1 months), and only two people had surgical excision in the third year of follow-up.

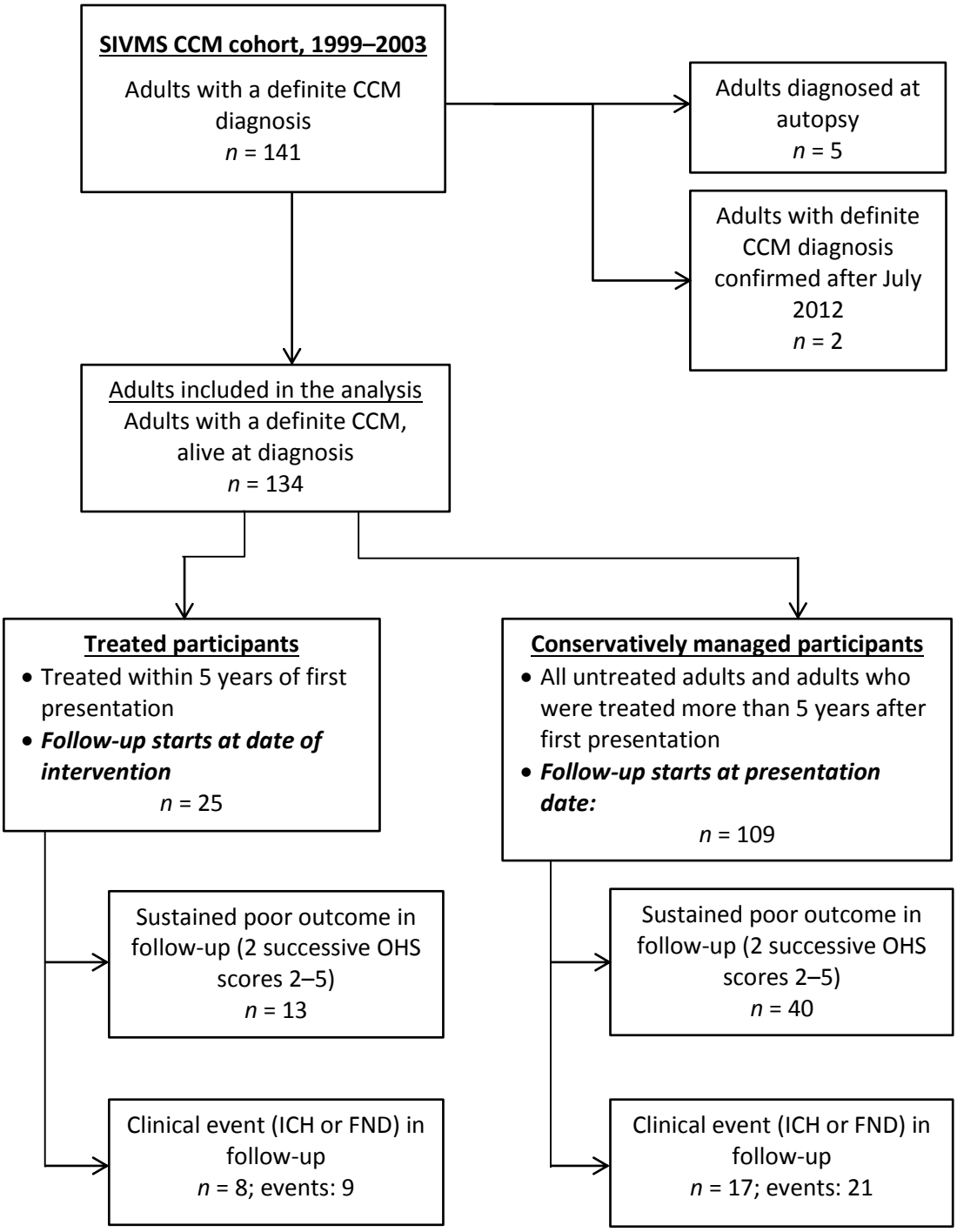



**Figure 5.1 Flowchart of adults included in the analysis**

In the treated group, 21 adults underwent surgical excision of their lesion: 20 had a single CCM excised, and another participant had two lesions excised on different occasions. Two of the remaining four adults had a partial resection, and in one case the lesion was excised six weeks later (follow-up started at partial resection for both participants). Another two adults underwent haematoma evacuation, one of whom had a subsequent excision nine months later; for the latter participant, follow-up began immediately after the excision of his lesion.

### 5.4.2 Baseline characteristics

Baseline characteristics of the cohort, stratified by treatment group, are shown in Table 5.3. A male : female sex ratio of 2 : 3 was identical in both groups. A larger percentage of the untreated group harboured a brainstem lesion (15% *vs* 4%), but fewer people who were conservatively managed had multiple lesions (16% *vs* 24%). Comparing symptoms that led to a CCM diagnosis in the two groups, a larger percentage of the treated group presented with haemorrhage (32% *vs* 9%) and seizure (40% *vs* 23%), and conversely fewer presented incidentally (12% *vs* 51%). Two adults in the treated group, however, initially presented incidentally, but one experienced a haemorrhage and the other a focal neurological deficit in the period of untreated follow-up between presentation and intervention; presentation type and age at presentation for these two participants were adjusted to take account of these clinical events in untreated follow-up.

When type of presentation was dichotomized into ICH and FND versus incidental and seizure, a larger percentage of adults in the treated group presented with an intracranial haemorrhage or focal neurological deficit (48% *vs* 26%) ($\chi^2(1) = 4.84$, $p = 0.033$). However, those who were conservatively managed tended to be almost a decade older at the time of presentation (median age 43 years *vs* 34 years in the treated group) (Mann-Whitney test, $p = 0.004$). Despite these baseline imbalances, the dichotomized OHS scores at presentation were similar in both groups: 44% in the treated group had an OHS score 0–1 compared with 51% in the conservatively managed group.

**Table 5.3 Baseline characteristics of adults who presented with a definite diagnosis of cerebral cavernous malformation in Scotland, 1999-2003, stratified by treatment group**

| Characteristic | Treated group, *n* = 25 | | Conservatively managed group, *n* = 109 | | Statistical tests |
|---|---|---|---|---|---|
| | *n* | *%* | *n* | *%* | |
| Sex: | | | | | |
| Female | 15 | *60%* | 64 | *59%* | Female *vs* male: OR = 1.06 (0.44–2.56) |
| Male | 10 | *40%* | 45 | *41%* | |
| Age at presentation* (median, IQR) | 34 | *26.5, 41.5* | 43 | *33.5, 53.0* | Mann-Whitney U test ($p$ = 0.004) |
| CCM location: | | | | | |
| Lobar | 19 | *76%* | 71 | *65%* | Brainstem *vs* other location: |
| Cerebellum | 4 | *16%* | 14 | *13%* | OR = 0.24 (0.03–1.92) |
| Deep | 1 | *4%* | 8 | *7%* | |
| Brainstem | 1 | *4%* | 16 | *15%* | |
| CCM multiplicity: | | | | | Single *vs* multiple: OR = 0.59 (0.20–1.68) |
| Single | 19 | *76%* | 92 | *84%* | |
| Multiple | 6 | *24%* | 17 | *16%* | |
| Mode of clinical presentation* | | | | | ICH + FND *vs* incidental + seizure: |
| Incidental | 3 | *12%* | 56 | *51%* | OR = 2.67 (1.09–6.53) |
| Seizure | 10 | *40%* | 25 | *23%* | $\chi^2(1) = 4.84$ (p = 0.033) |
| Intracranial haemorrhage | 8 | *32%* | 10 | *9%* | |
| Focal neurological deficit | 4 | *16%* | 18 | *17%* | |
| Oxford Handicap Scale at presentation: | | | | | OHS 0–1 *vs* OHS 2–6: |
| 0–1 | 11 | *44%* | 55 | *51%* | OR = 0.77 (0.32–1.85) |
| 2–5 | 14 | *56%* | 54 | *50%* | |

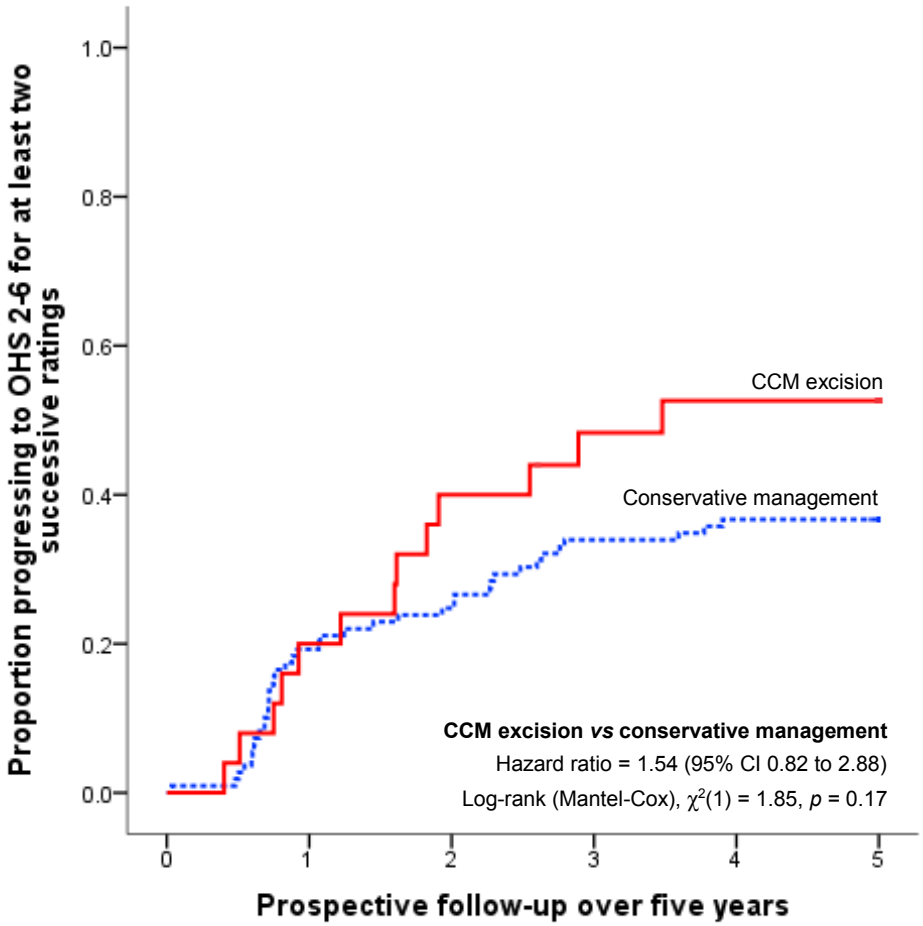
*Mode of clinical presentation and age at presentation have been adjusted for the six adults who experienced an ICH or FND before they underwent surgery.

### 5.4.3 Primary outcome

The primary outcome of this analysis was sustained poor outcome, a functional outcome measure defined as two successive Oxford Handicap Scale scores 2–5 (see Table 5.2). Of the 25 adults who underwent surgery, 13 (52%) had a period of sustained poor outcome within five years of the intervention, compared with 40 adults (37%) in the conservatively managed group ($n$ = 109) who had a similar period of sustained poor outcome within five years of presentation.

As can be seen in the Kaplan-Meier survival plot in Figure 5.2, there was no strong evidence that progression to a period of sustained poor outcome differed between the two groups during the five years of follow-up (log-rank test (Mantel-Cox) $\chi^2(1) = 1.85$, $p$ = 0.17). Although there is a suggestion of a trend in favour of conservative management, it is possible that this might become less apparent if the length of follow-up were increased. In the univariate Cox regression analysis to compare the effect of treatment (surgical excision versus conservative management) on functional outcome, the hazard ratio (HR) was 1.54 (95% confidence interval 0.82 to 2.88). It should be noted, however, that this progression to sustained poor outcome was unadjusted for potential confounders and, as can be seen from Table 5.3, there were clear differences between the two treatment groups at presentation. In Table 5.4, the number of adults who progressed to sustained poor outcome, stratified by treatment group and baseline characteristic, is displayed. The corresponding adjusted results are presented in Table 5.9 in section 5.4.5.

The spectrum of dependence, measured on the Oxford Handicap Scale, is shown in Figure 5.3 and illustrates fluctuations in functional outcome over the follow-up period. The OHS score at presentation date is displayed for both groups, together with the annual OHS scores of adults whose family doctors participated in the study during the five-year follow-up period (which started from presentation for the conservatively managed group and from the date of intervention for the treated group). In several instances of missing annual OHS scores, family doctors responded to the annual questionnaire that they felt unable to rank functional outcome of their patient on the grounds that they had not seen him/her over the previous year.




| Adults at risk (events in previous year) | | | | | | |
|---|---|---|---|---|---|---|
| **Treated** | 25 | 20(5) | 15(5) | 12(2) | 11(1) | 11(0) |
| **Untreated** | 109 | 88(21) | 82(6) | 72(10) | 69(3) | 68(0) |

Sustained poor outcome is defined as an OHS score of 2–6 for at least two successive ratings.

**Figure 5.2 Kaplan-Meier estimate of progression to sustained poor outcome (primary outcome), stratified by treatment group, during five years of prospective follow-up**

**Table 5.4 Sustained poor outcome, stratified by treatment group and baseline characteristic**

| Baseline characteristic | Category | CCM excised (tx) | | | Conservatively managed (cm) | | |
|---|---|---|---|---|---|---|---|
| | | Sustained poor outcome | | Total | Sustained poor outcome | | Total |
| | | *n* | *%* | $n_{tx}$ | *n* | *%* | $n_{cm}$ |
| **Treatment group** | | 13 | *52%* | 25 | 40 | *37%* | 109 |
| **Mode of presentation** | ICH/FND | 5 | *42%* | 12 | 10 | *36%* | 28 |
| | Other | 8 | 62% | 13 | 30 | *37%* | 81 |
| **CCM location** | Brainstem | 1 | *100%* | 1 | 9 | *56%* | 16 |
| | Other | 12 | *50%* | 24 | 31 | *33%* | 93 |
| **Sex** | Male | 5 | *50%* | 10 | 21 | *47%* | 45 |
| | Female | 8 | *53%* | 15 | 19 | *30%* | 64 |
| **CCM multiplicity** | Single | 9 | *47%* | 19 | 31 | *34%* | 92 |
| | Multiple | 4 | *67%* | 6 | 9 | *53%* | 17 |
| **OHS rating at presentation** | 0–1 | 6 | *55%* | 11 | 10 | *18%* | 55 |
| | 2–5 | 7 | *50%* | 14 | 30 | *56%* | 54 |
| **Age-group at presentation** | < 40 years | 7 | *41%* | 17 | 13 | *28%* | 47 |
| | 40+ years | 6 | *75%* | 8 | 27 | *44%* | 62 |

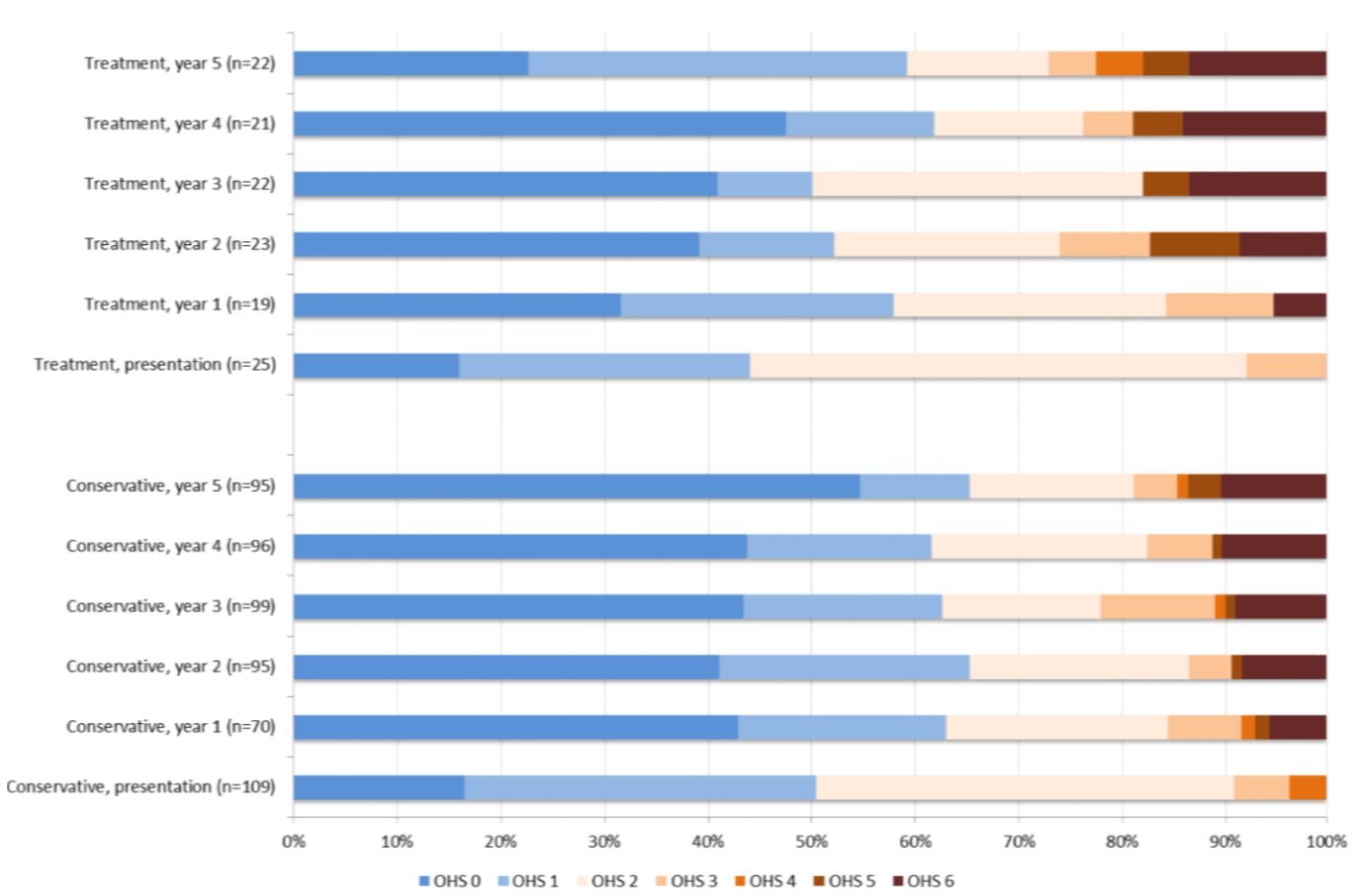



**Figure 5.3 Dependence, measured on the Oxford Handicap Scale, for adults with CCM diagnosis, from date of presentation: five-year follow-up period from presentation for conservatively managed group and from intervention for CCM excision group**

The Oxford Handicap Scale is frequently dichotomized into favourable outcome, which may be categorized as OHS 0–1 (or 0–2), versus unfavourable outcome, OHS 2–6 (or 3–6); hence in Figure 5.3, the blue bars represent OHS scores 0–1 and the orange bars OHS 2–6. Both treated and conservatively managed groups had a similar distribution of scores at presentation. For each of the five years of follow-up, however, at least 40% (range 41–55%) of the conservatively managed group received an OHS rating of 0, whereas a lower percentage (between 23% and 48%) of the treated group were allocated OHS score 0. When OHS scores of 0–1 were considered, the difference between the two groups was less pronounced, particularly in years 4 and 5 of follow-up.

## Completeness of OHS ratings

As was described in section 5.3.5 above, the primary outcome measure of sustained poor outcome was computed using the annual Oxford Handicap Scale ratings that were reported by participants' family doctors each year. The level of completeness for these ratings is shown in Table 5.5 below; the mean level of completeness over the six years is similar for both treatment groups (85%).

**Table 5.5 Completeness of annual GP Oxford Handicap Scale ratings, stratified by treatment group**

| Year | Conservative management | | CCM excision | |
|---|---|---|---|---|
| | *n* | *%* | *n* | *%* |
| 1 | 70 | *64%* | 19 | *76%* |
| 2 | 95 | *87%* | 23 | *92%* |
| 3 | 99 | *91%* | 22 | *88%* |
| 4 | 96 | *88%* | 21 | *84%* |
| 5 | 95 | *87%* | 22 | *88%* |
| 6 | 100 | *92%* | 21 | *84%* |
| Mean | 93 | *85%* | 21 | *84%* |

### 5.4.4 Secondary outcome

The secondary outcome was a composite endpoint – the first occurrence in follow-up of intracranial haemorrhage, new focal neurological deficit or cerebral infarction; this was considered as a potential explanatory outcome. There were 42 clinical events – intracranial haemorrhage or new focal neurological deficit – after initial presentation, but no occurrences of infarction in this cohort.

Eight adults (32%) in the treated group (three of whom had had at least one clinical event between presentation and intervention), and 17 (16%) in the untreated group experienced a clinical event in follow-up (see Table 5.6). Three FNDs, however, occurred more than five years after presentation (one to an adult in the conservatively managed group, who had a lobectomy more than seven years after presentation, and two within six weeks to an adult who had undergone surgical excision 6.5 years previously). The number of adults who experienced a clinical event during five-year follow-up, stratified by treatment group and baseline characteristic or measurement, is presented in Table 5.7.

#### Conservatively managed group

Among the participants who were conservatively managed (see Table 5.6, two suffered a single haemorrhage, a third experienced two haemorrhages and the fourth adult two haemorrhages and a focal neurological deficit; all haemorrhages were attributable to the CCM. The median time to first haemorrhage in the conservatively managed group was 1.6 years, with an interquartile range of 0.9–3.6 years. In addition, 13 participants experienced at least one focal neurological deficit (median time to first FND: 1.5 years, IQR: 0.6–2.3 years). Eight FNDs were attributable to the CCM, and five were possibly due to the lesion; one adult experienced two FNDs, both possibly due to the CCM.

**Table 5.6 Clinical events within five-year follow-up period**

| Treatment group | Type of event | Event due to: | Number of adults | Notes | Earlier events before intervention | Subsequent events after recurrence[a] |
|---|---|---|---|---|---|---|
| **Treated** | ICH | procedure | 1 | | – | 1 adult x 1 FND |
| | FND | IVM | 1 | | 1 adult x 1 FND + 2 ICH | – |
| | FND | procedure | 6 | | 1 adult x 1 ICH | – |
| | | | | | 1 adult x 1FND | – |
| **Conservatively managed** | ICH | IVM | 4 | 1 fatal | – | – |
| | | | | | – | 1 adult x 1 ICH |
| | | | | | – | 1 adult x 1 ICH + 1 FND |
| | FND | IVM | 8 | – | – | – |
| | FND | Probably IVM | 5 | | | 1 adult x 1 FND |
| **Total** | ICH | | 5 | | | 2 |
| | FND | | 20 | | | 3 |

[a] In addition, two other women experienced events more than six years after the start of follow-up:
one was in the conservatively managed group, but had an excision more than seven years after presentation and suffered an FND due to the procedure;
the second experienced two FNDs within six weeks, more than six years after surgical excision.

**Table 5.7 First occurrence of ICH or new FND in follow-up, stratified by treatment group and baseline characteristic or measurement**

| Baseline characteristic | Category | CCM excised | | | Conservatively managed | | |
|---|---|---|---|---|---|---|---|
| | | Clinical event in follow-up | | Total | Clinical event in follow-up | | Total |
| | | *n* | *%* | *n* | *n* | *%* | *n* |
| **Treatment group** | | 8 | *32%* | 25 | 17 | *16%* | 109 |
| **Mode of presentation** | ICH/FND | 4 | *33%* | 12 | 11 | *39%* | 28 |
| | Other | 4 | 31% | 13 | 6 | *7%* | 81 |
| **CCM location** | Brainstem | 1 | *100%* | 1 | 8 | *50%* | 16 |
| | Other | 7 | *29%* | 24 | 9 | *10%* | 93 |
| **Sex** | Male | 4 | *40%* | 10 | 3 | *7%* | 45 |
| | Female | 4 | *27%* | 15 | 14 | *22%* | 64 |
| **CCM multiplicity** | Single | 3 | *16%* | 19 | 14 | *15%* | 92 |
| | Multiple | 5 | *83%* | 6 | 3 | *18%* | 17 |
| **OHS at presentation** | 0–1 | 3 | 27% | 11 | 7 | *13%* | 55 |
| | 2–5 | 5 | *36%* | 14 | 10 | *19%* | 54 |
| **Age-group at presentation** | < 40 years | 5 | *29%* | 17 | 7 | *15%* | 47 |
| | 40+ years | 3 | *38%* | 8 | 10 | *16%* | 62 |

### Treated group

In the treated group, one adult sustained a haemorrhage two days after surgery (and over two years later experienced a non-haemorrhagic focal neurological deficit), and seven adults experienced a focal neurological deficit: four the day after first intervention, one the day following excision of a second lesion, one 8 days after surgery, and one two months later. Seven of the clinical events in this group could be attributed to the intervention; the eighth participant had a focal neurological deficit attributable to the CCM two months after a haematoma evacuation, following three previous events (FND and 2 ICH) in untreated follow-up (see Table 5.6).

### Untreated follow-up period in treated group

In the period between presentation and first intervention, six adults (24%) suffered at least one clinical event (see Table 5.8): three participants experienced a single FND; a fourth sustained a single ICH; a fifth sustained two ICH; and the sixth suffered a single FND, followed by two ICH. For these six adults, the date of the last event before excision was taken as 'presentation' date: baseline characteristics of age and type of presentation were adjusted to the final event before treatment.

**Table 5.8 Clinical events experienced between presentation and first intervention**

| Adults | Type of clinical event(s) |
|---|---|
| 3 | Single FND |
| 1 | Single ICH |
| 1 | Two ICH |
| 1 | Single FND followed by two ICH |

### 5.4.5 Analysis

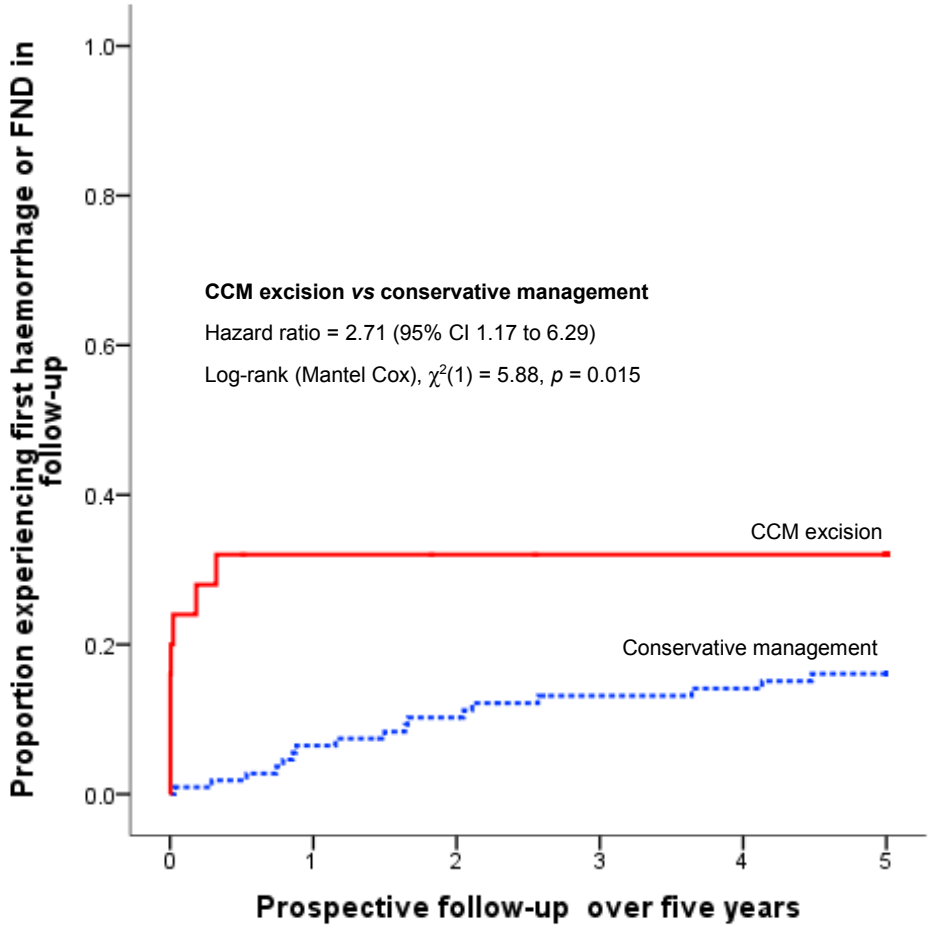
The Kaplan-Meier survival curve for progression to first clinical event in follow-up is shown in Figure 5.4. There was a greater risk of a first event in follow-up for the treated group (log-rank test (Mantel-Cox) $\chi^2(1) = 5.88$, $p = 0.015$), and the hazard ratio was 2.71 (95% confidence interval 1.17 to 6.29). It is striking, however, that clinical events in the treated group occurred within a few days of surgery, whereas events in the conservatively managed group occurred throughout the five years of follow-up.

#### Univariate and multivariable analyses

Four potential confounders, based on baseline imbalance and epidemiological evidence, were pre-specified: age at presentation, mode of clinical presentation, CCM location and sex. Univariate Cox regression was performed to obtain a hazard ratio for treatment group and each confounder in order to observe the effect of each on the primary and secondary outcomes (Table 5.9).

For the primary outcome, in which the difference in time to sustained poor outcome was examined, none of the five variables achieved significance, although the hazard ratio for increasing age (at presentation or at final event preceding treatment) per year was 1.015 (95% CI 0.998 to 1.03).

However, when time to first clinical event (the secondary outcome) was examined, three variables achieved significance: treatment group, prior clinical event and CCM location. The hazard ratio for treatment (CCM excision versus conservative management) was 2.71 (95% CI 1.17 to 6.29); the hazard ratio for presentation (ICH or FND versus other presentation) was 4.03 (95% CI 1.81 to 8.97); and the hazard ratio for CCM location (brainstem versus other location) was 4.46 (95% CI 1.96 to 10.12).




| Adults at risk (events in previous year) | | | | | | |
|---|---|---|---|---|---|---|
| **CCM excision** | 25 | 16(8) | 15(0) | 14(0) | 14(0) | 14(0) |
| **Conservative management** | 109 | 100(7) | 95(4) | 88(3) | 87(1) | 85(2) |

**Figure 5.4 Kaplan-Meier estimate of progression to ICH/FND (secondary outcome), stratified by treatment group, during five years of prospective follow-up**

Cox regression was used to investigate the effect of treatment on both functional and clinical outcome, after adjusting for the four potential confounders, and these results are also summarized in Table 5.9 (right column). These results should be interpreted with a degree of caution, however, since the proportional hazards assumption could not be assessed, due to the paucity of events in the analysis.

**Table 5.9 Univariate and multivariable analyses of first progression to the first occurrence of a primary or secondary outcome during five years of prospective follow-up**

| | Univariate analyses HR (95% CI) | Multivariate analyses HR (95% CI) |
|---|---|---|
| **Primary outcome – sustained poor outcome** | | |
| Excision *vs* conservative management | 1.54 (0.82 to 2.88) | 2.19 (1.12 to 4.29) |
| Increasing age (at presentation or at final event preceding treatment), per 10 years | 1.16 (0.98 to 1.37) | 1.23 (1.02 to 1.48) |
| ICH or FND at presentation *vs* incidental or seizure | 0.88 (0.48 to 1.59) | 0.68 (0.35 to 1.30) |
| Brainstem *vs* other location | 1.77 (0.89 to 3.53) | 2.51 (1.18 to 5.34) |
| Female *vs* male | 0.64 (0.37 to 1.09) | 0.56 (0.32 to 0.97) |
| **Secondary outcome – clinical event** | | |
| Excision *vs* conservative management | 2.71 (1.17 to 6.29) | 3.60 (1.29 to 10.03) |
| Increasing age (at presentation or at final event preceding treatment), per 10 years | 1.03 (0.79 to 1.33) | 1.10 (0.81 to 1.48) |
| ICH or FND at presentation *vs* incidental or seizure | 4.03 (1.81 to 8.97) | 2.12 (0.85 to 5.26) |
| Brainstem *vs* other location | 4.46 (1.96 to 10.12) | 4.15 (1.52 to 11.37) |
| Female *vs* male | 1.87 (0.78 to 4.48) | 1.27 (0.51 to 3.16) |

**Notes**

The analyses for the primary outcome have been conducted using the adjusted time-period: sustained deterioration for the untreated group is deemed to have occurred in the middle of the period between the date of the last OHS 0–1 score and the first of at least two consecutive OHS 2–6 scores.

After adjusting for increasing age at presentation (or at final event preceding treatment), ICH or FND versus incidental or seizure at presentation, brainstem versus other location, and female versus male, the hazard for progression to sustained poor outcome for those whose lesions were excised was more than twice that for those who were conservatively managed (HR = 2.19, 95% CI: 1.12 to 4.29). Thus adjusting for these potential confounders and imbalances at baseline has resulted in a slightly increased hazard ratio, which now also achieves significance (univariate HR = 1.54, 95% CI 0.82 to 2.88).

Similarly, after adjusting for the four potential confounders, the hazard for progression to first clinical event in follow-up for those who received surgery was more than three times that for those who were conservatively managed (HR = 3.60, 95% CI: 1.29 to 10.03). Again, the size of the hazard ratio after adjustment was made for baseline imbalances and potential confounders has slightly increased from the univariate value of 2.71 (95% CI 1.17 to 6.29).

### Deaths

Thirteen participants died during the five-year follow-up period. Among the ten deaths in the conservatively managed group, two were attributable to IVM and eight to other causes; in the treated group, one death was attributable to the cavernous malformation and two to other causes. There were no deaths within thirty days of treatment. The median age at death was 60 years (interquartile range 50 to 73 years): this was substantially younger for those whose cavernous malformation was excised (51 years) compared to those who were conservatively managed (66 years).

### 5.4.6 Sensitivity analyses

In the sensitivity analyses for the secondary outcome, progression to intracranial haemorrhage or new focal neurological deficit, events that were possibly attributable to a CCM were excluded from the analysis. This resulted in five clinical events – all new FND – being removed from the original analysis. Although one of these adults had a second event in follow-up, this FND was also probably due to the CCM, and so excluded from the sensitivity analysis. All excluded FND occurred to adults who had been managed conservatively. Therefore, in this sensitivity analysis:

(i) 25 adults had a CCM excised**:**

8 had an event within 5 years of excision;

17 had no event within 5 years of excision;

(ii) 109 adults were managed conservatively**:**

12 had an event in 5-year follow-up period;

97 had no event in 5-year follow-up period.

The results of the univariate and multivariable analyses are presented in Table 5.10. In the univariate analysis, treatment, CCM location and ICH/FND presentation are still statistically significant, with hazard ratios slightly increased, as would be expected. In addition, in the multivariable analysis, ICH/FND presentation is also statistically significant, together with treatment and CCM location (which were before). The unadjusted and adjusted hazard ratios for treatment versus conservative management are larger than in the original analysis, since all the events excluded in the analysis were in the conservatively managed group.

**Table 5.10 Sensitivity analysis: univariate and multivariable analyses of progression to first clinical event during five years of follow-up**

| Secondary outcome[a] – clinical event | Univariate hazard ratio (95% CI) | Multivariable adjusted hazard ratio (95% CI) |
|---|---|---|
| Excision *vs* conservative management | 3.78 (1.54 to 9.26) | 5.54 (1.78 to 17.23) |
| Increasing age above mean, per 10 years | 1.01 (0.76 to 1.36) | 1.14 (0.81 to 1.61) |
| Presentation with haemorrhage or FND | 6.12 (2.35 to 15.94) | 3.03 (1.05 to 8.76) |
| Brainstem CCM location | 5.09 (2.08 to 12.50) | 5.17 (1.67 to 16.01) |
| Female | 1.69 (0.65 to 4.41) | 0.98 (0.35 to 2.71) |

[a] The secondary outcome was an ICH or new FND, attributable either to a CCM or surgery.

## 5.5 Discussion

In this prospective, population-based observational cohort study of the management of adults with cavernous malformations, interventional treatment was a predictor of progression to sustained poor outcome, after adjustment had been made for factors imbalanced at baseline (increasing age and intracranial haemorrhage or focal neurological deficit at presentation) and/or potentially related to CCM prognosis (brainstem lesion and sex). Progression to sustained poor outcome was not adequately explained by progression to first clinical event in follow-up.

### 5.5.1 Strengths

#### Study design

The main strength of this study is its meticulous study design and multiple attempts to minimize several potential sources of bias (see subsections 4.2.2 and 5.3.4 above). Prospective recruitment to the cohort was restricted to newly diagnosed cases of

cerebral cavernous malformation in a stable adult population in 1999 of 4.08 million inhabitants (Scotland), using multiple overlapping sources of case ascertainment, to counter potential selection bias. Strict diagnostic criteria and outcome definitions were employed in an attempt to avoid detection and misclassification biases.

Prospective follow-up was undertaken using multiple overlapping sources at annual intervals and is still continuing; 100% completeness of baseline data and 97% completeness of follow-up was achieved over the five-year duration of this study; assessors were blinded to potential prognostic features; and functional outcome was measured on a validated scale. In addition, because a single study population was stratified during follow-up into concurrent treated and conservatively managed groups, problems that would arise from comparing different geographical populations originating from different ethnic backgrounds at different time periods have been avoided. This study represents current clinical practice, and can be compared at a future date with a second cohort of adults from the same geographical area, who were diagnosed with cerebral cavernous malformation between 2006 and 2010 inclusive.

### 5.5.2 Limitations

#### Non-random treatment allocation

The main weakness of this study is the fact that, since it is an observational study, there is potential confounding of results by certain imbalances at presentation: the treated group were younger and more likely to present with haemorrhage or focal neurological deficit than the conservatively managed group. From a clinical perspective, it is not surprising that the treated group contains younger patients with more severe symptoms, since this group is most likely to derive the greatest future benefit from interventional treatment with the least risk, as its members probably have fewer comorbidities and a longer life expectancy. It should be noted, however, that rankings on the OHS were similar in both groups at presentation.

In an attempt to limit the problem of confounding, multivariable analysis was used to adjust for the imbalances in the baseline characteristics (see Table 5.9 for the hazard

ratios and 95% confidence intervals). Randomization of treatment allocation, however, is required as it is the only effective method of ensuring that no systematic difference exists among patients in either treatment group before the treatment is started (Hlatky et al., 1988, Byar, 1991). Although in this study adjustment has been made for baseline characteristics that are suspected or known to affect outcome, it is possible that other – unobservable or unknown – factors may exist (for example, genetic factors), that have an effect on outcome; randomization increases the probability that such factors would be evenly distributed among treatment groups.

## Size of treated group

Further limitations of this study are the small size of the treated group (19%), which reflects current clinical practice in Scotland, and the comparatively short follow-up period. Both of these shortcomings, however, can be addressed in the future, since the second cohort of adults, diagnosed between 2006 and 2010 inclusive, is being followed, and follow-up still continues for the first cohort.

## Oxford Handicap Scale ratings

### *Different time points for two treatment groups*

A potential problem with the primary outcome measure is that the Oxford Handicap Scale ratings for the two treatment groups start at different time points. Although the OHS rating occurs annually, those who have received interventional treatment receive their first rating at some point between 5–18 months after surgery, whereas those who have been conservatively managed are rated sometime after the approximate anniversary of their diagnosis. To avoid the spurious implication that progression to sustained poor outcome was about six months slower for conservatively managed participants, a date midway between last OHS score 0–1 and first OHS score 2–6 was calculated and used for the start date of sustained poor outcome. This approach was justified since sustained deterioration tends to be a gradual process and is thus unlikely to occur on a specific date.

The fact that the time between intervention and first OHS rating is not fixed can also lead to potential difficulties: for example, a patient may have a first OHS score 2–5 at three months after intervention, which is ignored according to our criteria, and a second rating which is also OHS 2–5, followed by subsequent ratings that are OHS 0–1. In this example, the patient is deemed not to have suffered sustained poor outcome; however, had the first score, three months after surgery, been used, then this patient would have been included in the subgroup that experienced a period of sustained poor outcome.

*Influence of a patient's comorbidity on OHS rating*

Another potential problem associated with the primary outcome measure in this study is that a general practitioner's annual OHS rating of his/her patient's functional outcome may be unduly influenced by the individual's comorbidity. In theory, the OHS rating represents an annual assessment of the level of independence that an adult diagnosed with a cavernous malformation enjoys. In practice, however, it represents a single snapshot once a year of how a general practitioner assesses his/her patient's functional outcome. It may not take into account any of the patient's other health problems. For example, an asymptomatic patient may be diagnosed incidentally with a cavernous malformation at the time of an MRI for traumatic brain injury; in subsequent years, his OHS rating may signify poor functional outcome, but this may conceivably be due to disability resulting from the brain injury rather than to problems associated with the presence of a cavernous malformation. This problem is more likely to affect older patients, since the risk of suffering from many diseases, e.g. cardiovascular disease, cancer, etc., tends to increase with age.

## 5.5.3 Other points

### Possibility of subsequent improved outcome

It should also be noted that although 13 adults (52%) in the treated group and 40 (37%) in the conservatively managed group experienced a period of sustained poor outcome within the first five years of follow-up, there is a suggestion that this is not necessarily a permanent state and that improvement may be possible at a later date. Taking two successive OHS scores 0–1 as evidence of a period of sustained improvement, following the period of sustained poor outcome, 14 (26%) of the 53 adults who suffered a period of sustained poor outcome subsequently enjoyed a period of sustained improvement later during the course of seven years of follow-up. In terms of treatment groups, nine of the 40 adults (23%), who were conservatively managed and had a period of sustained poor outcome, subsequently enjoyed a period of good outcome; similarly, five of the 13 participants (38%) whose lesion was excised and had a period of poor outcome showed sustained good outcome. The number of adults in either group is too small, however, to permit any meaningful conclusions being drawn from this treatment-group stratification, beyond a demonstration that a period of sustained poor outcome for either treatment group is not necessarily a permanent state.

## 5.5.4 Summary

In this chapter an exploratory observational study comparing outcomes of adults who either opted for CCM excision or conservative management is described. The strengths and limitations of the study were presented in subsections 5.5.1 and 5.5.2 above, and need to be assessed carefully. On the one hand, the adults were drawn from a prospective population-based cohort study that was very carefully designed to minimize several sources of potential bias, and follow-up was assiduously accumulated; on the other hand, the lack of randomization of the two groups is a

serious flaw in the study design. In addition, although the two treatment groups were concurrent, the number of adults who received interventional treatment was relatively small ($n$ = 25).

For these reasons, the results of this study should be treated with a great deal of caution. They would appear to imply that complications within days of interventional surgery may outweigh the benefits of excision. Furthermore, although none of the adults whose CCMs were excised without early surgical complications suffered a subsequent ICH or FND within five years of surgery, their level of dependence, as measured by Oxford Handicap Scale scores – especially in the fourth and fifth years since surgery – was similar to that of the group who were conservatively managed. (Figure 5.3 suggests that the treated group, if anything, may have a slightly inferior outcome to the untreated group.) Additionally, cases have been reported of new CCMs growing after excision and subsequently bleeding. It is also possible, however, that adults in the conservatively managed group may suffer a subsequent ICH or FND more than five years after presentation, although results in SIVMS and other research suggest that clinical events tend to cluster in the early years and decline later.

However, the lack of treatment randomization, the small size of the surgery group, and the fact that dependence levels in either group may be due to the effects of comorbidities rather than CCM militate against drawing a clear conclusion from this study, other than to repeat the case for a randomized controlled trial (RCT). As is discussed in Chapter 10 below, recruitment to a potential RCT in this area will certainly not be without its difficulties, as individuals may understandably be reluctant to leave the decision to undergo neurosurgery purely to chance. In the meantime, the recommended guidelines for the management of adults with CCMs – whether the CCMs were incidentally detected with no clinical events in follow-up, CCMs that have caused one or more than one ICH or FND – is to decide management on a case-by-case basis (Poorthuis et al., 2013, Samarasekera et al., 2012).

# Chapter 6: Methods for the individual patient data meta-analysis

## 6.1 Background

Over the past two decades, a number of papers describing the clinical course of untreated cavernous malformations have been published (Robinson et al., 1991, Zabramski et al., 1994, Aiba et al., 1995, Kondziolka et al., 1995, Kim et al., 1997, Porter et al., 1997, Moriarity et al., 1999, Porter et al., 1999, Barker II et al., 2001, Hasegawa et al., 2002, Mathiesen et al., 2003, Wang et al., 2003, Ghannane et al., 2007, Al-Shahi Salman et al., 2012, Flemming et al., 2012, Schneble et al., 2012). Unfortunately, many of these studies suffer from one or more biases, as was discussed in Chapter 3 above (section 3.3.1): most were hospital-based studies, which are susceptible to selection bias; many were retrospective studies, which suffer from information bias; and in many cases detection and misclassification biases were likely, as diagnostic criteria were not clearly specified and outcome events, especially intracranial haemorrhage (Al-Shahi Salman et al., 2008), were undefined.

In addition, studies that limit outcome to intracranial haemorrhage may be at risk of detection bias, as outlined in Chapter 2 above (section 2.3.2). There is a tendency for clinicians to investigate the cause of a haemorrhage in young, normotensive adults, whereas older, hypertensive adults are less likely to be investigated, especially if they are known to harbour a cavernous malformation, and thus the possibility exists that a small haemorrhage may be missed. Patients with cavernous malformations who are being treated conservatively may be more reluctant to report minor symptoms to their clinicians, who in turn may be more reluctant to arrange radiographic investigation,

even though the symptoms may in some cases reflect a small symptomatic haemorrhage, which would have been detected, had the appropriate neuro-imaging been undertaken. In some instances, of course, the reverse may be true: some patients being treated conservatively may report minor symptoms more frequently, if they are anxious about the management of their disease, in the hope that the treatment decision may be changed.

Diagnosis of a haemorrhage also relies on timely neuro-imaging using the appropriate modality: for example, a haemorrhage can only be detected on a CT scan if it is performed within a week of the event; if more than a week has elapsed between the haemorrhage and the CT scan, the blood can no longer be detected, even though a haemorrhage occurred. Thus for the reasons described above, some researchers combine outcomes of intracranial haemorrhage and focal neurological deficit into a composite endpoint of 'clinical event' (Porter et al., 1997, Al-Shahi Salman et al., 2012).

The main limitations of previously published studies, however, have been small sample size and short follow-up; this has resulted in some studies being underpowered with an insufficient length of follow-up for infrequent outcomes to occur.

## 6.2 Risk of intracranial haemorrhage after cerebral cavernous malformation diagnosis

Comparison of the risks of ICH between these studies is problematic for several reasons. First, some research groups restricted inclusion in their study to selected participants: for example, those patients who initially presented with a haemorrhage or FND that led to their eventual CCM diagnosis; or individuals who had the familial form of the disease, and who frequently have multiple lesions; or individuals with a CCM in a specific anatomical location. The risk of ICH or FND in follow-up is likely to be different for each group.

Second, different statistical methods have been used to calculate risk of ICH or FND in untreated follow-up in most of the studies. In many papers, authors calculated the risk of ICH assuming that the CCM is congenital, whereas it is now accepted that lesions do occur de novo during lifetime (Zabramski et al., 1994, Kattapong et al., 1995, Detwiler et al., 1997, Nimjee et al., 2006). In some studies, the risk per lesion was estimated rather than that per patient. In other studies, the total number of ICH in follow-up rather than the first ICH in follow-up was used to calculate an annual rate; it was also assumed that the annual rate is constant over time, which appears not to be the case, as some studies have evidence of a gradual diminishing of risk over time (Barker II et al., 2001, Al-Shahi Salman et al., 2012).

Furthermore, the risk of haemorrhage is affected by the increased availability of more sophisticated neuro-imaging techniques over the past twenty years; not only are more symptomatic cavernous malformations being detected, but intracranial haemorrhages can also be detected more reliably since the development of haemosiderin-sensitive MRI sequences (Josephson and Al-Shahi Salman, 2011).

Overall, the annual rates of first-ever ICH (0.3% to 2.0%) have been lower than recurrent ICH (6.2% to 18.3%) from the same lesion, but neither of these rates has been estimated with precision (Al-Shahi Salman et al., 2012, Flemming et al., 2012).

## 6.3 Aims of an individual patient data meta-analysis

Most studies have consistently identified the occurrence of a prior haemorrhage as a risk factor for an adult developing a subsequent haemorrhage. Studies have varied, however, in whether putative risk factors such as patient sex, CCM location or CCM multiplicity have influenced the risk of ICH. Therefore, the patient's and clinician's dilemma about whether, when and how to treat a cavernous malformation would be informed by more precise estimation of the clinical course of untreated cavernous malformations, the identification of prognostic factors, and the derivation and evaluation of a prognostic model. By collaborating with other research groups and

conducting an individual patient data meta-analysis, it was possible to use consistent methods of analysis for all patients across studies and to investigate two outcomes: ICH alone and a composite outcome of ICH and new focal neurological deficit.

The aims of this study were to improve the precision of previous estimated risks of first ICH after CCM diagnosis (and also the composite outcome of first or recurrent ICH or FND), and to identify prognostic factors for such an outcome after diagnosis. Finally, if it were appropriate, a prognostic model based on several covariates would be developed and evaluated / validated.

### 6.3.1 Study questions

The rationale for this individual patient data meta-analysis was to help the clinician when explaining a CCM diagnosis to a patient and to inform their decision on an appropriate management strategy for the disease. This study aims to answer the following three questions:

1. What is the estimated risk of an untreated adult suffering an ICH (or a clinical event, that is, either an ICH or FND) within five years of CCM diagnosis?
2. Which baseline characteristics modify the risk of ICH (or clinical event) occurring within five years of CCM diagnosis?
3. Is it possible to predict, at the time of diagnosis, an individual's risk of a subsequent ICH (or clinical event)?

## 6.4 Cohorts

After conducting a systematic review, described elsewhere (Al-Shahi Salman et al., 2012), thirteen suitable studies were identified that could provide detailed individual patient data regarding clinical outcome (ICH or FND) between diagnosis and either CCM treatment or last follow-up. A protocol was sent to each research group, together

with an invitation to participate in an individual patient data meta-analysis. The invitation was also extended to two research groups whose studies were unpublished at the time (Flemming et al., 2012, Schneble et al., 2012).

### 6.4.1 Study and participant eligibility

Our criteria for study eligibility for inclusion in this collaboration were that each study should have a minimum sample size of 50 adults; the period at risk should begin either at first CCM diagnosis or the symptoms leading to CCM diagnosis, thereby enabling calculation of an event risk from diagnosis (not retrospective 'lifetime risk'); symptomatic ICH should be included as an objective, pre-defined clinical outcome; and outcome events should be able to be quantified per patient during the follow-up period.

The minimum sample-size criterion was dictated by time and patient-number constraints. It is very time-consuming to liaise with different research groups, understand data collection methods and clean datafiles, and as the two outcomes (ICH and FND) are comparatively uncommon, a minimum study size was stipulated to maximize the chance of obtaining datasets with at least some outcome events and thereby avoid spending a disproportionate length of time with very small datasets that would make a minimal contribution to the study.

As mentioned above, many of the early studies describing the natural history of cavernous malformations calculated the risk of haemorrhage over the course of an individual's life-time. However, this method of calculation underestimates the risk of haemorrhage, because it is now recognized that cavernous malformations are dynamic lesions that can appear de novo, as well as increase or diminish in size over time (Zabramski et al., 1994, Pozzati et al., 1996, Nimjee et al., 2006, Flemming et al., 2011). Even among individuals in whom no new lesions have developed, calculation of haemorrhagic risk from the date of diagnosis is more appropriate, since in many cases a lesion will have been latent for many years and will suddenly become active, resulting in an event that leads to its diagnosis.

In addition, the following individual inclusion criteria were specified: each participant should be aged 16 years or older and have received a definite CCM diagnosis, validated by brain MRI; and participants should not have received interventional treatment – surgical excision or stereotactic radiotherapy – by the time of diagnosis.

## 6.5 Procedures

The following baseline data were requested from collaborating studies: patient sex, date of birth, date and mode of clinical presentation leading to CCM diagnosis, date of earliest radiographic-definite CCM diagnosis, number and location of CCM, and presence of associated developmental venous anomalies. Dates of all clinical outcome events (ICH or FND) during follow-up, dates and types of any interventional treatment, and date and cause of death were also requested.

As in previous chapters, distinctions were made between intracranial haemorrhage, non-haemorrhagic focal neurological deficit (where there is no evidence of recent blood on timely brain neuro-imaging or pathological examination) and focal neurological deficit not otherwise specified (where neither neuro-imaging of the appropriate modality nor pathological examination had been performed at all or at the correct time to be able to distinguish recent blood), according to published criteria (Al-Shahi Salman et al., 2008), for clinical events both at presentation and in follow-up (see section 2.3.2). Initial presentation was categorized as 'incidental' if an adult was asymptomatic or if their symptoms (e.g. headache or tinnitus) could not be ascribed to the underlying cavernous malformation. Initial presentation was classified as epileptic seizure if the seizure was neither symptomatic of a concomitant intracranial haemorrhage nor more likely to be due to another cause.

Unlike in the previous two chapters, the inception point for this study was taken as the date of first-in-a-lifetime diagnosis of a cavernous malformation, and the follow-up period was five years. The two primary outcome events were symptomatic ICH alone and a composite endpoint of symptomatic ICH or new FND. The composite outcome

(referred to forthwith as a 'clinical event') is important, because both ICH and FND have a similar level of morbidity for the patient, and in certain circumstances an outcome labelled FND may, in reality, be an ICH, but not categorized as such, either because the appropriate neuro-imaging was not performed or because the imaging failed to detect any blood (Al-Shahi Salman et al., 2008).

## 6.6 Statistical analysis

### 6.6.1 Preparing the data for analysis

A protocol and a separate detailed statistical analysis plan were developed and agreed with all the participating centres before data analysis began (see Appendices B and E). The data from each study were checked carefully for internal consistency and agreement with any relevant published reports, and any queries were referred back to the original research group for clarification. Individuals in each cohort were checked to ensure that they met the eligibility criteria to be included in the study. Datafiles for each cohort were created in identical format to enable the data for individual cohorts to be merged into a single large dataset.

In instances where adults harboured multiple cavernomas, a single primary location was attributed to the symptomatic lesion; however, where an adult presented asymptomatically with multiple cavernous malformations, brainstem location took precedence (see sections 4.2.5 and 4.3 above). Location of cavernoma was categorized as brainstem (in the midbrain, pons or medulla), cerebellar, deep (in the thalamus, basal ganglia or choroidal), or lobar (in the cortex or subcortical areas of the cerebral hemispheres) in the baseline characteristics, but in the univariate and multivariable analyses the covariate was dichotomized to brainstem versus other location. Similarly, mode of presentation has four categories at the baseline level (ICH, FND, seizure or incidental), but was dichotomized to presentation with ICH or FND versus other presentation (i.e. incidental or with seizure) for analysis.

### Missing data

During the process of cleaning each dataset, problems of missing data were addressed by contacting the clinician responsible for providing the data. In the statistical analysis plan, it was reported that in cases where missing data could not be resolved they would be imputed, if appropriate.

## 6.6.2 Descriptive analysis

As a first stage, tables of baseline characteristics were compiled for each individual cohort and also for the pooled cohorts; these were stratified by mode of clinical presentation, to enable the similarity of each cohort at inception to be assessed. In time-to-event analyses, the primary outcome was ICH and the secondary outcome was clinical event; follow-up data were censored for each adult at the time of the earliest occurrence of the treatment, death or last follow-up; if censoring had not already occurred, follow-up was truncated at five years after CCM diagnosis.

The decision to truncate follow-up at five years was influenced by several factors. A reasonable length of follow-up was required for each cohort to provide an opportunity for outcome events to occur, since intracranial haemorrhage and focal neurological deficit are not common events. However, there is some evidence that clinical events tend to cluster within a few years of diagnosis, and then the event rate declines (Barker II et al., 2001, Al-Shahi Salman et al., 2012). In an ideal study, all cohorts would have a pre-determined fixed length of follow-up; unfortunately, this was not possible in this study, as the end of the recruitment period for the second Scottish cohort was 31 December 2010. Thus five years seemed an optimum compromise between being a sufficient length of time to enable the majority of clinical events occurring in follow-up to be captured, on the one hand, and being a reasonable target length for studies to achieve. It is hoped that five years might become a standard follow-up period to enable comparison of present results with those of future studies.

It should be noted that the possibility of the occurrence of informative censoring cannot be excluded, since a neurosurgeon may discern that a patient's condition is worsening and thus decide to excise the CCM before an intracranial haemorrhage or focal neurological deficit actually occurs. Censoring at interventional treatment is discussed at greater length in section 8.3 in Chapter 8 below.

### 6.6.3 Identification of risk factors

Five predictors of haemorrhage or clinical event within a five-year follow-up period were pre-specified on account of their clinical significance and existing evidence base (Robinson et al., 1991, Aiba et al., 1995, Kondziolka et al., 1995, Moriarity et al., 1999, Josephson and Al-Shahi Salman, 2011, Al-Shahi Salman et al., 2012, Flemming et al., 2012), in addition, to their completeness, accuracy and reliability. Mode of clinical presentation and CCM location were core predictors; sex, CCM multiplicity (multiple versus solitary) and age were putative predictors. In addition, CCM size and associated developmental venous anomaly were pre-specified as exploratory predictors, if they had been recorded by sufficient cohorts.

In both the univariate and multivariable analyses, age was treated as a continuous variable, since categorization of a continuous variable results in loss of information, power and precision (Royston et al., 2006). To enable survival plots to be inspected for age, the pooled cohort was divided into three, approximately equal, age-groups.

Kaplan-Meier survival curves, stratified by each of the five pre-specified covariates in turn, displayed the cumulative proportion of the cohort that experienced each of the outcome events over five years of follow-up (Kirkwood and Sterne, 2003, Machin et al., 2006). The log-rank test was used to compare the survival plots for each predictor.

Cox proportional hazards regression was used in the univariate analyses to determine the unadjusted hazard ratios for each predictor of both intracranial haemorrhage and clinical event within five-year follow-up (Machin et al., 2006). Assuming the proportional hazards assumption was not violated, multivariable Cox proportional

hazards regression would be used to model the risk of a future ICH (and ICH or FND, where the data were available) for an adult with CCM during untreated follow-up (Harrell et al., 1996, Machin et al., 2006). In the multivariable analyses for each outcome event, the two core predictors – mode of clinical presentation and CCM location – were entered into the model first, and then each putative predictor – sex, CCM multiplicity and age – was added in turn to ascertain whether any of them added statistically significant prognostic information over and above the two core predictors.

### 6.6.4 Study design of IPDMA

In a meta-analysis the results of several similar studies are combined into a single summary statistic (with confidence interval). The rationale for undertaking an individual patient data meta-analysis (IPDMA) is to synthesize the available evidence concerning the clinical course of untreated cerebral cavernous malformations to improve the estimated risk of an intracranial haemorrhage within five years of CCM diagnosis, and to identify risk factors for this outcome.

Although meta-analyses can be performed using aggregate data (summary statistics), it is more satisfactory to use individual patient data in time-to-event analyses since the researcher is not only interested in whether an outcome occurred, but at what point in the follow-up period it occurred. Also, when individual patient data are used, the researcher is able to compare participant characteristics across studies and investigate heterogeneity (Tudur Smith, 2004). In addition, as was outlined above (in section 6.2), the risk of an intracranial haemorrhage has not been estimated in a standardized manner in the other studies reported in the systematic review (Al-Shahi Salman et al., 2012), and therefore it would not be appropriate to carry out a meta-analysis using aggregate data from these studies.

A brief résumé of the IPDMA methodology used in this study follows in the next subsection.

## Theory: meta-analysis

### *Two-stage vs one-stage approach*

Before undertaking an individual patient data meta-analysis, thought must be given to which model should be used – whether fixed effect or random effects – and whether the meta-analysis should be carried out in one or two stages. In the two-stage approach, data for each study are analysed independently, using the same method of analysis, to produce summary statistics, together with confidence intervals (first stage). The summary statistics calculated for each study (i.e. aggregate data) can then be synthesized according to standard meta-analysis techniques (second stage).

In the one-stage approach, individual patient data from all the studies in the meta-analysis are pooled and a single model, stratified by study, is fitted (Riley et al., 2010). However, the one-stage method relies on a much stronger assumption of homogeneity among studies than the two-stage method, and it is also more challenging to implement for time-to-event data, especially when the random-effects model is used (Bowden et al., 2011), since hierarchical regression models would be required (Stewart et al., 2012).

In the present study, the two-stage meta-analysis method was adopted, as it would be beneficial to be able to inspect the hazard ratios in individual studies as well as the pooled cohorts. Indeed, this approach is arguably more transparent than the one-stage, especially when considerable heterogeneity between studies is likely: not only were patients in the cohorts located in different countries, with different health-care systems, but some studies were hospital-based whereas others were population-based.

### *Fixed-effect model*

In the fixed-effect model, it is assumed that no heterogeneity exists between studies and that there is one underlying true parameter value (or common effect size, hence the name ‘fixed effect’) for all the studies; any differences in observed estimates of the

parameter can be attributed solely to sampling variation (Deeks et al., 2001, Kirkwood and Sterne, 2003, Borenstein et al., 2009). The summary estimate of the pooled log hazard ratio is a weighted average of the log hazard ratios from each of the *k* individual studies:

$$\log(\mathrm{HR}_F) = \frac{\sum_{i=1}^{k}[w_i \times \log(\mathrm{HR}_i)]}{\sum_{i=1}^{k} w_i}$$

where $\log(\mathrm{HR}_F)$ is the log hazard ratio under the fixed-effect model (in which it is assumed that the mean hazard ratio is the same for each study in the meta-analysis), and $\log(\mathrm{HR}_i)$ is the log hazard ratio for study *i*. The relative weight, $w_i$, is calculated as the inverse of the sampling variance of the mean of study *i*; therefore studies with greater precision have a smaller variance and greater weight, and so have greater influence in the meta-analysis. Conversely, studies that have a wider dispersion and larger variance, and are thus less precise, have a lower weight and consequently less influence in the meta-analysis.

*Random-effects model*

By contrast, in the random-effects model it is assumed that heterogeneity does exist between studies. Thus the true parameter (e.g. log hazard ratio) for each study will vary around an overall average value, and is assumed to be part of a random sample from a normal distribution, i.e.

$$\log(\mathrm{HR}_i) \sim N(\log(\mathrm{HR}_R), \tau^2)$$

where the mean, $\log(\mathrm{HR}_R)$, is the true 'overall' log hazard ratio, and the between-study variance is $\tau^2$. In addition, for each study, the observed effect will be different to the true effect, due to sampling error. Therefore in the random-effects model, the distance between the true mean parameter value and the observed summary statistic is composed of two parts: the true variation in effect sizes (between-study variability) and the variation due to sampling error (i.e. chance) (within-study variability) (Tudur Smith, 2004, Borenstein et al., 2009).

The random-effects summary estimate of the log hazard ratio is

$$\log(\mathrm{HR}_R) = \frac{\sum_{i=1}^{k}[w_i^* \times \log(\mathrm{HR}_i)]}{\sum_{i=1}^{k} w_i^*}$$

where $w_i^*$ is the weight assigned to study *i* in the random-effects model:

$$w_i^* = \frac{1}{v_i + \tau^2}$$

and $v_i$ is the within-study variance for study *i* (and is therefore equal to $w_i^{-1}$) (Kirkwood and Sterne, 2003, Borenstein et al., 2009, Thompson et al., 2010, Tudur Smith, 2004). The standard error of the random-effects summary estimate is the square root of the inverse of the sum of the adjusted weights:

$$\mathrm{s.e.}(\log(\mathrm{HR}_R)) = \sqrt{\frac{1}{\sum_{i=1}^{k} w_i^*}}$$

The between-studies variance, $\tau^2$, is estimated using the DerSimonian and Laird method (also known as the method of moments) (DerSimonian and Laird, 1986):

$$\tau^2 = \tau_{DL}^2 = \max\left[0, \left(\frac{Q - df}{W}\right)\right]$$

where, in a meta-analysis with *k* studies, *Q* is the test statistic for the $\chi^2$ test of heterogeneity with *k* - 1 degrees of freedom, *df*, i.e.

$$Q = \sum_{i=1}^{k} w_i[\log(\mathrm{HR}_i) - \log(\mathrm{HR}_F)]^2$$

and

$$W = \sum_{i=1}^{k} w_i - \left(\frac{\sum_{i=1}^{k} w_i^2}{\sum_{i=1}^{k} w_i}\right).$$

In random-effects models, the intention is that by allocating weights, both sources of variance should be minimized. The range of the weights assigned to studies is narrower than for a fixed-effect model, and the sum of the weights is always equal to 100%.

Therefore smaller studies tend to exercise a greater influence in random-effects models than in the fixed-effect models (and conversely larger studies are less influential), because in a random-effects model the mean of a distribution of effects, rather than a single effect, is being estimated.

Compared with fixed-effect models, the summary estimate in random-effects models tends to be more conservative, with a wider confidence interval; this reflects the fact that in the random-effects model there is greater uncertainty because, in addition to the sampling variation, the true effect is assumed to vary between studies (Kirkwood and Sterne, 2003, Borenstein et al., 2009).

### Cerebral Cavernous Malformation study

In the present study, two-stage random-effects meta-analyses were performed for each of the five *a priori* predictors. The random-effects model was used because of the probability that clinical heterogeneity existed between the studies. The `metan` command in Stata, which uses the DerSimonian-Laird method (DerSimonian and Laird, 1986), was used to perform the meta-analyses in this thesis (Bradburn et al., 2009, Harris et al., 2009).

Forest plots displayed the unadjusted hazard ratios for each cohort and an unadjusted hazard ratio for the pooled study. The meta-analyses were repeated, this time using the adjusted hazard ratios; hazard ratios for the two core predictors were adjusted for each other, and the hazard ratios for each of the three putative predictors were adjusted for the two core predictors.

## 6.6.5 Heterogeneity

Heterogeneity is an important consideration, both from the clinical and statistical perspectives, and in this study there are three potential sources. A first source of heterogeneity is in the study design (methodological heterogeneity): adults in a population-based study may be more likely to present incidentally than adults in a

hospital-based study. To account for this source of heterogeneity, the total dataset was stratified by study design – that is, population-based cohort versus hospital based cohort.

A second source of heterogeneity may be found in the baseline characteristics of participants (clinical heterogeneity), and of particular concern in this study are patient age, sex, mode of clinical presentation, CCM location and multiplicity, as these may influence outcome. For example, patients in a tertiary referral neurosurgery unit may be more likely to harbour brainstem lesions, and patients in an institute specializing in genetics may be more likely to have the familial form of the disease, with multiple lesions, than patients in general hospitals or the community.

A third type of heterogeneity that might exist between the cohorts is due to the variation in the true effect size between studies (statistical heterogeneity); this might make pooling the hazard ratios and the derivation of an overall prognostic model questionable.

### Theory: heterogeneity

The sources of observed variation in effect size can be split into two components: first, observed effects that vary due to within-study error (i.e. when all studies have the same – i.e. true – effect size and thus heterogeneity does not exist), and second, the real heterogeneity in effect size (when the effect size varies between studies) (Borenstein et al., 2009).

Several tests have been devised to discern the extent of heterogeneity in meta-analysis. Until recently, a frequently used test for heterogeneity was the Cochran's *Q* test, which is the weighted sum of squares of deviations (as given in the subsection above Theory: meta-analysis):

$$Q = \sum_{i=1}^{k} w_i \left[\log(\mathrm{HR}_i) - \log(\mathrm{HR}_F)\right]^2$$

The null hypothesis is that there is a fixed effect shared by all ($k$) studies, and the test statistic, $Q$, is compared with a $\chi^2$ distribution with ($k - 1$) degrees of freedom.

The $Q$ test, however, is not reliable at detecting true heterogeneity between studies, since it lacks power when the meta-analysis consists of a small number of studies or small studies that contain large within-study variance (Hardy and Thompson, 1998, Deeks et al., 2001, Higgins et al., 2003, Borenstein et al., 2009, Huedo-Medina et al., 2006). Thus a $p$-value greater than 0.05 does not necessarily imply homogeneity; indeed, some authors recommend using a 10% cut-off for significance testing to assess heterogeneity (i.e. $p < 0.1$), but that in turn creates problems by increasing the risk of a type I error (Higgins et al., 2003). Another parameter used to quantify heterogeneity is $\tau^2$, the variance of the true effect sizes or between-study variance (see subsection Theory: meta-analysis above).

The $I^2$ index measures the percentage of total variation in study estimates that is due to true (between-study) heterogeneity, rather than chance (Higgins and Thompson, 2002):

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

The range of possible values for $I^2$ lies between 0% and 100%, so if the degrees of freedom ($k - 1$) are greater than $Q$, then $I^2$ is set at 0%. When $I^2$ is equal to 0%, there is no observed heterogeneity; the level of heterogeneity increases as the value of $I^2$ increases.

An advantage of using $I^2$ is that it is independent of the number of studies in the meta-analysis. $I^2$ is the ratio of excess $(Q - df)$ to total $(Q)$ dispersion, and can be considered as a measure of inconsistency across study findings since it reflects the extent of the overlap of confidence intervals (Higgins and Thompson, 2002, Higgins et al., 2003, Huedo-Medina et al., 2006, Borenstein et al., 2009, Bowden et al., 2011). Higgins and Thompson (2003) include guidance for calculating the standard error of $I^2$, which they use to calculate 95% uncertainty intervals. Higgins and co-authors have

tentatively suggested that for $I^2$ values of 25%, 50% and 75%, heterogeneity might be considered to be respectively mild, moderate and high (Higgins et al., 2003).

### 6.6.6 Sensitivity analysis

Sensitivity analyses were undertaken. For the outcome of ICH, all the cohorts were pooled, and the univariate and multivariable Cox regression analyses were repeated on the entire dataset, stratified by the covariate 'study'. For the composite outcome of clinical event (ICH or FND), the cohorts where FND was recorded were pooled and the Cox regression analyses were repeated as above, stratified by 'study'.

### 6.6.7 Building a prognostic model

The level of heterogeneity between the cohorts was examined for each covariate, and possible reasons were proposed to explain its existence. If heterogeneity between cohorts were sufficiently modest to enable a prognostic model to be built, patient data in all cohorts would be pooled to form a single dataset (Altman et al., 2009, Hemingway et al., 2013, Riley et al., 2013, Steyerberg et al., 2013, Steyerberg, 2009). Ideally, this pooled dataset should be split in half, with one half being used to develop the model and the other to evaluate or validate it. However, as outcome events for this condition are comparatively uncommon, it would be unlikely that there would be sufficient events in each portion to build or evaluate a model. If it were not possible to use one or more cohorts in developing the model, then these could possibly be used to validate it (Altman et al., 2009, Debray et al., 2012, Moons et al., 2012b, Moons et al., 2012a, Steyerberg et al., 2013).

Assuming the proportional hazards assumption were not violated, multivariable Cox proportional hazards regression would be used to model the risk of a future ICH (and ICH or FND, if the data were available) occurring within five years of CCM diagnosis during untreated follow-up. This model is expressed in terms of the hazard function,

$h(t)$, which is the instantaneous rate of an event happening at time *t*, given that it has not occurred up to time *t*:

$$h(t) = h_0(t)\exp(b_1x_1 + b_2x_2 + \cdots + b_px_p)$$

$h_0(t)$ is the baseline or underlying hazard function, when all the covariates have the value of 0; $x_1$ to $x_p$ are the covariates in the model; and $b_1$to $b_p$ are the regression coefficients; values for $h_0(t)$, $b_1$and $b_p$ are all estimated from the data (Harrell et al., 1996, Machin et al., 2006).

Pre-specified covariates in the model would be selected for their clinical significance: covariates of *a priori* interest were listed above, namely, ICH/FND at presentation, brainstem location, age (as a continuous variable), lesion multiplicity, and sex. Other potential covariates include lesion size and associated developmental venous anomaly. Initially, the two core predictors were entered into the model first and then each putative predictor was added in turn to examine its impact on the outcome. The Wald test was used to assess the contribution of each covariate, and whether it should be included in the final model. The Wald test is based on the ratio of the regression coefficient to its standard error, i.e.

$$W = \left[\frac{b}{\mathrm{SE}(b)}\right]^2$$

where *W* has a $\chi^2$ distribution, with one degree of freedom.

Since there is inconsistency in the literature about the role of sex as a putative risk factor for ICH or FND, the four other *a priori* covariates were forced into the model on account of their clinical significance, regardless of their statistical significance in the univariate analyses; the analysis was re-run with sex included, to ascertain its effect on the outcome.

If heterogeneity between the cohorts were substantial, but the proportional hazards assumption were not violated, then the Cox proportional hazards regression would be stratified by a 'study' covariate, with covariates of *a priori* interest included in the model (Hosmer et al., 2008, Steyerberg, 2009, Fibrinogen, 2009).

### 6.6.8 Prognostic index

If appropriate, a prognostic index would be developed to enable classification of the patients into three groups: low-, medium- and high-risk of experiencing an intracranial haemorrhage (or clinical event) within five years of diagnosis. The index would take the form:

$$\text{prognostic index score} = b_1x_1 + b_2x_2 + \cdots + b_px_p$$

where, again, $x_1$ to $x_p$ are the covariates, and $b_1$ to $b_p$ the regression coefficients, estimated from the data (Machin et al., 2006).

One of the main reasons for creating this index would be for its use as an aid for clinicians at the time of CCM diagnosis: to enable them to advise patients of their estimated five-year risk of ICH (ICH or FND) following diagnosis, if they were conservatively managed. Therefore the covariates in the index must be readily available at time of diagnosis. It is also essential to ensure that the levels for each variable are ordered in the same direction, probably from tending towards a good prognosis (low code) to tending towards a bad prognosis (high code). If this form of coding is used, then a high score in the prognostic index will indicate a poor prognosis.

After the covariates have been selected and a suitable model obtained, the next step would be to simplify the regression coefficients of the model. This is normally achieved by finding a common factor and then rounding each coefficient to the nearest integer, or by dividing all the regression coefficients by the smallest coefficient and then rounding. Finally, a prognostic index would be developed by calculating a prognostic score for each adult in the dataset.

A frequency distribution of the individual scores would be examined, and two cut-off points would be used to separate the dataset into high-, medium- and low-risk categories (Machin et al., 2006, Leonard et al., 1991). The cut-off points can either be

determined at arithmetically convenient points, or by selecting, for example, the lower and upper quartiles for the 25% with worst prognosis, and 25% with the best prognosis, respectively. A Kaplan-Meier plot, stratified by these three risk categories, would then be examined to determine the degree of discrimination achieved by the index.

### 6.6.9 Subsidiary analysis

In the original analysis of the earlier Scottish cohort (Al-Shahi Salman et al., 2012), the four adults who had a recurrent haemorrhage in follow-up were all women, and 16 of the 17 adults who experienced a recurrent clinical event in follow-up were women; with this in mind, the possibility of exploring the influence of sex on recurrent haemorrhage and/or focal neurological deficit in a subsidiary analysis was pre-specified in the statistical analysis plan. (It should be noted, however, that in the original analyses, inception was date of presentation, whereas in this study inception is date of diagnosis.)

Two new datasets were created: the first consisted of adults who had either presented with an intracranial haemorrhage or experienced one within five years of diagnosis, after presenting with a focal neurological deficit, seizure or incidentally, and the outcome was a (recurrent) ICH within five years of diagnosis. The second dataset included participants who had either presented with an ICH or FND or had suffered one within five years of diagnosis, after presenting with a seizure or incidentally, and the outcome event in this dataset was clinical event. Kaplan-Meier survival curves, stratified by sex, were inspected and the log-rank test was used to compare the curves for each sex.

# Chapter 7: Cohorts included in the individual patient data meta-analysis

## 7.1 Introduction

Thirteen research groups were identified in a systematic review (Al-Shahi Salman et al., 2012) and invited to join the collaboration (see Appendix C). One group agreed to collaborate and successfully shared their data; three groups agreed to collaborate, but the data-sharing stage was never reached; one group was difficult to contact, and when this was eventually achieved, the research group had disbanded and the data were not available; another group no longer had access to the original data; and seven did not respond to several invitations. Among the twelve teams who did not share their data, six cohorts (544 patients) were highly selected: one was a small study of adults with familial cavernous malformations (21 subjects), two cohorts only included patients who had bled at presentation (218 adults), and three cohorts studied adults with brainstem cavernomas (305 patients). Inclusion of these six cohorts would have skewed the results, since mode of clinical presentation and CCM location are both core predictors of ICH or FND outcome. Of the remaining six cohorts (n = 527), five groups published their studies on or before 1997.

In addition to those research teams identified in the systematic review, several other well-known active research groups were contacted and invited to join the collaboration. In total, data were received from five cohorts: three research groups based at tertiary-care referral centres (Toronto Western Hospital, Canada; Mayo Clinic, Rochester, MN, USA; and Hôpital Lariboisière, Paris, France), in addition to data from a single prospective population-based group with two different time-windows for recruitment (Scottish Intracranial Vascular Malformation Study).

**Table 7.1 Studies invited to join the collaboration**

| Study | Date | Number of patients | Type of study | Type of patients |
|---|---|---|---|---|
| Robinson | 1991 | 66 | Retrospective; hospital-based | |
| Zabramski | 1994 | 21 | Prospective; hospital-based | Familial CCM |
| Aiba | 1995 | 110 | Retrospective; hospital-based | |
| Kondziolka | 1995 | 122 | Retrospective + prospective; hospital-based | Conservative management |
| Kim | 1997 | 62 | Retrospective; hospital-based | |
| Porter* | 1997 | 110 | Retrospective + prospective; brain IVM unit | |
| Moriarity | 1999 | 68 | Prospective; hospital-based | |
| Porter | 1999 | 100 | Retrospective; hospital-based | Brainstem |
| Barker | 2001 | 136 | Retrospective; hospital-based | Bled at presentation |
| Hasegawa | 2002 | 82 | Retrospective + prospective; radiosurgery unit | High-risk, bled at presentation; pre-treatment |
| Mathiesen | 2003 | 68 | Retrospective + prospective; hospital-based | Brainstem + deep |
| Wang | 2003 | 137 | Retrospective; hospital-based | Brainstem |
| Ghannane | 2007 | 79 | Retrospective; hospital-based | |
| Flemming* | 2012 | 292 | Retrospective; tertiary-care referral centre | |
| Schneble* | 2012 | 87 | Retrospective; tertiary-care referral centre | |
| Al-Shahi Salman* | 2012 | 135<br>160 | Two prospective, population-based studies, different years | |

*These studies accepted the invitation to collaborate.

## 7.2 Hospital-based cohorts

### 7.2.1 Mayo Clinic

Mayo Clinic is a tertiary-care referral centre situated at Rochester, Minnesota, USA; it provides integrated medical care not only for inhabitants of Rochester and the state of Minnesota, but also for individuals from all other US states and many countries throughout the world. Although the Mayo Clinic in Minnesota owns two hospitals for exclusive use of Mayo Clinic patients, most people with a CCM diagnosis are treated on an outpatient basis.

The Mayo Clinic cohort is a retrospective, hospital-based cohort. Clinicians searched the radiographic database and identified all patients with a CCM diagnosis, validated by MRI, who had attended the Mayo Clinic between 1989 and 1999, whether as an inpatient or outpatient (Flemming et al., 2012). Medical records were then scrutinized, and demographic and clinical information was recorded on standardized forms and entered into the computerized database for the CCM study.

The study inception point was time of CCM diagnosis, and follow-up was collected retrospectively. Between 2000 and 2003, the principal investigator undertook a clinical review of all the patients in the study: details of occurrence of symptomatic haemorrhage due to the CCM, pregnancy since diagnosis, surgery or stereotactic radiotherapy since diagnosis, and use of antithrombotic medication were all recorded in the study database; focal neurological deficit that occurred in follow-up, however, was not recorded. Because the Mayo Clinic is a tertiary-care referral centre, patients who had not been seen within six months of the clinical review were sent a postal questionnaire and then contacted by telephone for details of further follow-up; where available, medical records and radiographic film from other medical institutions were examined for follow-up information, which was duly recorded. Relatives of deceased patients were contacted for details about the cause of death on the death certificate.

In this cohort, haemorrhages that occurred in follow-up were categorized into three groups: definitive prospective, probable prospective and undocumented prospective. A definitive prospective haemorrhage was defined as 'a new clinical event (focal deficit, seizure or severe headache) in association with radiographic evidence of acute haemorrhage or autopsy data suggesting acute haemorrhage' (Flemming et al., 2012). A probable prospective haemorrhage was defined as a clinical event that suggested an intracerebral haemorrhage, but which was recorded in medical records obtained from a medical institution outwith the Mayo Clinic medical record system and the films were not available to Mayo Clinic clinicians to view. Finally, an undocumented prospective haemorrhage was an acute clinical event, but neither imaging report nor film was available to the researchers; often the information was acquired directly from the patient, and there was nothing documented in the patient's medical records about the episode. In this meta-analysis, only definitive and probable prospective haemorrhages were included in the analysis.

### 7.2.2 Toronto Western Hospital

Toronto Western Hospital is a tertiary-care referral centre situated close to the centre of the most populous city in Canada. It is a world leader in neuroscience and was one of the first hospitals in Canada to use gamma knife radiotherapy. In 1989, the Toronto Brain Vascular Malformation Study Group was formed and research on the natural history of cerebral cavernous malformations was published in 1997 (Porter et al., 1997). Most of the patients included in the Toronto Brain Vascular Malformation Study Group live in the Greater Toronto Area; the remaining patients predominantly live within Ontario, as it is very rare for a patient from a different Canadian province to be treated in the unit (Ronit Agid: personal communication).

All the patients in the Toronto cohort included in this study were referred to the Toronto Brain Vascular Malformation Study Group between 1989 and 2007; a very small number were diagnosed between 1987 and 1988. In all cases, the diagnosis of cerebral cavernous malformation was validated by brain MRI and, where available, pathological examination. Demographic and medical history was recorded by

clinicians on standardized data collection forms at the time of consultation. In 1993, the CCM database was computerized, using Microsoft Access software, and in 2000 an electronic patient record (EPR) system and the medical-imaging technology PACS (picture archiving and communication system) were set up.

Clinicians recorded both intracranial haemorrhage and non-haemorrhagic focal neurological deficit in follow-up. Haemorrhage was defined 'radiologically as acute or subacute blood located outside the hemosiderin ring or an increase in lesion size by 20% or more in diameter on serial imaging with associated mass effect and/or edema'. An event 'refers to neurological deterioration, defined as subjective worsening (new or increased neurological symptoms) accompanied by objective worsening of neurological findings, with or without radiologically proven hemorrhage' (Porter et al., 1997). In this cohort, no information on patient vital status was available.

Follow-up for patients in this cohort was prospective, but organized irregularly and only available if they attended an outpatient clinic appointment or were admitted to Toronto Western Hospital. Until about 2007, many patients were reviewed annually for several years, but some asymptomatic patients were seen only once. Around 2007, however, a decision was taken to abandon the annual review. Therefore patients referred to the clinic after this date have not been included in the present study, since their inclusion would almost certainly bias the meta-analysis: those patients recruited after 2007 who have follow-up are more likely either to have more problems related to their CCM diagnosis or be considered to be at greater risk of future events (to justify being reviewed) than those who have not been reviewed.

### 7.2.3 Hôpital Lariboisière, Paris

Hôpital Lariboisière in Paris is a tertiary-care referral centre, and all the patients in this cohort attended the Centre de Référence pour les maladies rares des Vaisseaux du Cerveau et de l'Oeil (CERVCO, the French national reference centre for rare neurovascular diseases of the eye and brain), located at the hospital. CERVCO provides a diagnostic service for hereditary neurovascular diseases for all French and

some European hospitals, and several research groups located there are conducting research on genetic neurovascular diseases. Because the genetic form of the disease is characterized by individuals harbouring multiple lesions, it is to be expected that this cohort will have a disproportionately high number of adults with multiple CCMs.

In October 2008, a database was set up and patients with a CCM diagnosis were enrolled into a prospective study; patients were reviewed at least annually, and more frequently, if the severity of their condition required it. Pre-specified demographic, clinical, genetic and radiological data were collected for patients with CCM. For adults who had been diagnosed before the database was set up, data at diagnosis and any clinical events that occurred in follow-up before October 2008 were collected retrospectively (Schneble et al., 2012).

The time of inception for this cohort was date of diagnosis. In this study, only CCM-related haemorrhages, defined according to the Angioma Alliance guidelines (Al-Shahi Salman et al., 2008), were recorded in follow-up.

## 7.3 Population-based studies

Two cohorts from the Scottish Intracranial Vascular Malformation Study (SIVMS), recruited between 1999 and 2003 (first cohort), and 2006 and 2010 (second), were included in this study. A description of how these cohorts were recruited is given in Chapter 4 above. It should be noted, however, that for the analyses in this part of the thesis, the point of inception for these studies is taken not as the date of presentation, as in Chapters 4 and 5, but as the date of diagnosis, so that consistency is maintained among all studies.

Although these two cohorts originated from the same population, they were analysed separately for two reasons. First, the length of follow-up period was not identical: participants in the earlier cohort had the potential to contribute five years of follow-up, whereas those diagnosed at the end of the final year in the later cohort were only able to contribute a maximum of 2.5 years follow-up because recruitment ended on 31

December 2010, and the cut-off date for data entry of follow-up was 19 July 2013 (see section 8.1 in Chapter 8). Second, neuro-imaging techniques are continuing to develop and become more sophisticated, and it was proposed that the individuals included in the second cohort might have slightly different characteristics to those in the first cohort. For example, in the first cohort 13% presented with an intracranial haemorrhage and 16% with a focal neurological deficit, whereas the corresponding percentages in the second cohort were 19% and 6% respectively, which might suggest that neuro-imaging techniques were becoming more adept at detecting small quantities of blood.

## 7.4 Datasets

The format of the original datasets for each cohort, data-cleaning methods that were employed and any difficulties that were encountered in the process are described in this section. Prior to requesting data from the four collaborating research groups, personalized questionnaires were sent to the clinicians and statisticians at each team, in an attempt to discover the form their data took and whether they would be suitable for inclusion in an individual patient data meta-analysis. (For copies of the questionnaires, please see Appendix D.)

### 7.4.1 Hospital-based cohorts

The data collected in the three hospital-based cohorts are systematically different to the data in the population-based cohorts. In the hospital-based cohorts, data have been collected in a much more haphazard manner, based on clinicians retrospectively reviewing case notes from patients who have attended clinic appointments, whereas the population-based cohorts are part of a national audit of intracranial vascular malformations that was set up for a specific purpose and for which follow-up is collected annually from family doctors and hospitals around the anniversary of CCM diagnosis.

## Mayo Clinic data

A copy of the anonymized dataset pertaining to the paper published in 2012 (Flemming et al., 2012) was received in November 2012. Three SAS files were included on the CD-ROM: one contained the data; a second the variable names and their coding on the four standardized case report forms; and the third was the value labels for the items in the case-report forms. All three files could be opened in IBM SPSS Statistics.

All queries relating to the data were referred back to the principal investigator, who was able to resolve all problems. For each participant, mode of presentation was re-examined and a new variable was created which was identical to that used in the Scottish cohorts. During the data-cleaning process, analyses were undertaken to replicate the tables in the paper published in 2012, and this was successfully achieved.

## Data from Toronto Western Hospital

At the request of the Toronto clinical research co-ordinator, a dummy dataset in Microsoft Excel was sent to Toronto as an example of the format and variables required. The anonymized data were received in a Microsoft Excel spreadsheet in September 2012, and subsequently imported into IBM SPSS Statistics.

### *Missing data*

In the Toronto datafile, there were three potential dates for inception: (i) 'date of onset of symptoms leading to CCM diagnosis'; (ii) 'date of earliest radiographic-definite CCM diagnosis'; and (iii) 'date of first attendance at the Vascular Malformation Clinic at Toronto Western Hospital', each of which had a number of missing values. The decision to use date of CCM diagnosis as inception was motivated by the fact that this date was most readily available in the other cohorts and, of the three possible dates in the Toronto data, it had the smallest number of missing values. Date of diagnosis was available for 318 (out of 345) participants, and all three dates were available for 228 adults.

**Table 7.2 Time between symptom-onset, diagnosis and referral for all participants in the Toronto cohort with three dates (*n* = 228)**

| Time period | Median (years) | Interquartile range (years) |
|---|---|---|
| Between symptom onset and diagnosis | 0.06 | 0 to 0.37 |
| Between diagnosis and referral | 0.14 | 0 to 0.36 |
| Between symptom onset and referral | 0.35 | 0.06 to 1.02 |

The difference in time between symptom-onset, diagnosis and referral was calculated for the 228 adults, and median and interquartile range for each time-period are presented in Table 7.2. For the 14 adults where the symptom-onset date was available, this date was used for inception, as it was closer to date of diagnosis than date of referral (in Table 7.2). However, where neither symptom-onset nor diagnosis dates were available ($n$ = 13), date of referral to Toronto Western Hospital was used as inception.

Unfortunately, deaths and thus mortality status were unavailable in this cohort, due to the method of data collection, which was driven by clinic attendance rather than by the research group requesting data at regular intervals from family doctors.

Although research from this group had been published previously (Porter et al., 1997), an earlier dataset had been used; thus analyses from this publication could not be replicated.

## Data from Hôpital Lariboisière, Paris

In response to a request for an anonymized datafile of patients with an MRI-validated CCM diagnosis and a minimum of one year follow-up, a Microsoft Excel spreadsheet of patients was received in June 2013; this was then imported into IBM SPSS Statistics.

Although the datafile received was purported to be that used in the paper published in 2012 (Schneble et al., 2012), the analyses could not be accurately reproduced. In the first instance, it was not obvious which of the patients had been included in the paper (104 were included in the datafile, but only 87 in the paper). Second, although the differences in baseline characteristics were small, the number of intracranial haemorrhages within five years of diagnosis was four (which was confirmed by the final author of the paper), with a fifth occurring in the sixth year, rather than the nine stated in the paper. Thus there were several discrepancies with what had previously been reported and the data that were received.

### 7.4.2 Population-based cohorts

The SIVMS database is stored in Microsoft Access, and an analysis application has been programmed to enable data extraction. Two anonymized datafiles were extracted from this database: the first, on 27 September 2013, for the 1999–2003 cohort, and the second, on 24 September 2013, for the 2006–2010 cohort. These extractions were exported via Microsoft Excel and imported into IBM SPSS Statistics.

### 7.4.3 Data completeness

#### Missing values

Upon pooling the five cohorts, the complete dataset consisted of 988 adults. After the five datasets had been checked and cleaned, there were no missing values for the following variables: date of birth, age at diagnosis, sex, mode of clinical presentation, CCM location and CCM multiplicity. For the two exploratory predictors, 5% of the values for associated developmental venous anomaly and more than 72% for CCM size were missing; however, there was uncertainty about whether the neuro-radiographers had consistently recorded the presence of associated developmental venous anomaly in some cohorts, and therefore it was not possible to include these two variables in the main analysis.

Date of diagnosis was missing for 27 adults in one cohort, but it was possible to substitute date of symptom onset leading to CCM diagnosis for 14 adults, and date of first attendance at study centre for the remainder (see subsection 7.4.1 above).

### Follow-up: completeness and maturity

Total follow-up, after censoring at first clinical event, intervention or death, and truncating at five years, was 3,232 patient-years. Using the Clark et al. equation for quantifying data completion – total observed follow-up as a percentage of the total potential follow-up – total observed follow-up represents 80% completeness of total potential follow-up (4,042 patient-years) (Clark et al., 2002). It should be recalled, however, that recruitment to the second Scottish cohort only finished on 31 December 2010, and therefore for some adults in that cohort it was possible to contribute only a maximum of 2.5 years; thus 100% completeness for five-year follow-up is not possible in this study (see end of section 8.1 below).

In an attempt to assess follow-up maturity (Machin et al., 2006), the length of follow-up for those who were censored in the original analysis was calculated: the median time was 4.24 years (interquartile range 1.95 to 5 years). By reversing the coding of the variable for outcome versus censored, a Kaplan-Meier plot of the proportion who still remained on follow-up was produced (see Figure 7.1). The estimated median length of follow-up for those who were originally censored was 4.51 years (95% confidence interval 4.44 to 4.57 years), and almost 47% of participants in the study were able to contribute data for the entire five-year follow-up period.

Of 96 adults in the entire study who did not experience an ICH or FND within five years of diagnosis and who had less than six months' follow-up, six died, 63 received interventional treatment, and 27 were lost to follow-up.

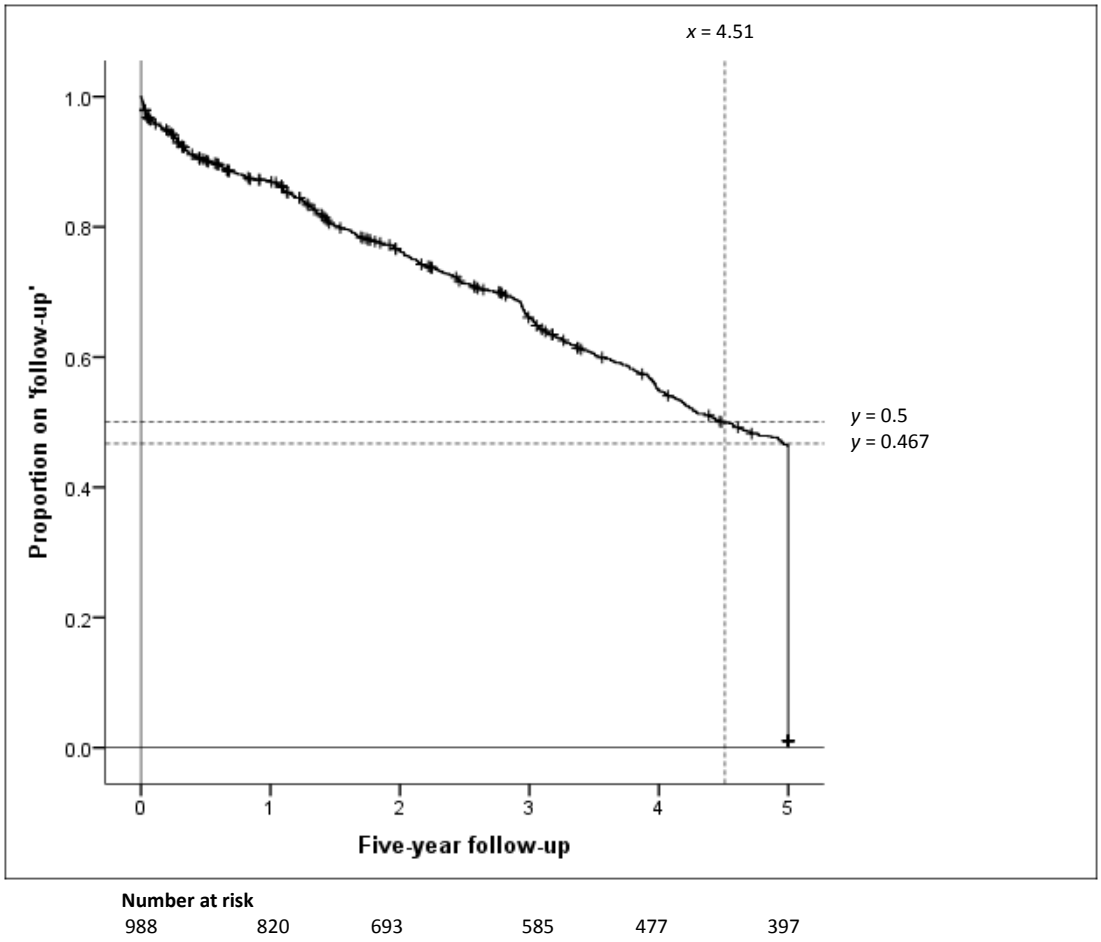



**Figure 7.1 Kaplan-Meier 'follow-up plot' for participants in the five cohorts**

## 7.5 Baseline characteristics of individual cohorts

### 7.5.1 Mayo Clinic cohort

In the original datafile, 292 patients had received a CCM diagnosis and had attended Mayo Clinic between 1989 and 1999, and 32 haemorrhages had been recorded. Some of these patients, however, did not meet the inclusion criteria for this study and their records were therefore removed from the datafile: for example, eight were treated on the day of diagnosis, three had no follow-up, five were treated before diagnosis and so were therefore not 'untreated', and nine were younger than 16 years of age at diagnosis (see the flowchart in Figure 7.2). In terms of number of outcomes, the four ICH that

were undocumented were removed, three ICH were lost because the patients had previously received treatment, another three occurred to patients who had been diagnosed in childhood, and two were lost through truncation of follow-up at five years after diagnosis. Hence in the present study, the Mayo Clinic cohort consisted of 267 adults, who had 20 haemorrhages within five years of diagnosis.

The baseline characteristics of this cohort are presented in Table 7.3. Slightly more than half were female (*n* = 143, 54%); of the symptoms that led to a CCM diagnosis, about a third (*n* = 98, 37%) presented incidentally, a quarter with ICH (*n* = 64, 24%), 29 (11%) with focal neurological deficit, and 76 (29%) with a seizure. The median age at diagnosis was 46 years (interquartile range 31–62 years), ranging from 40 years for those who presented with a seizure to 55 years for those presenting incidentally. Approximately a fifth of the cohort had multiple lesions (*n* = 49, 18%); a quarter of the primary lesions were located in the brainstem (*n* = 63, 24%), and of those with a brainstem CCM, 81% (*n* = 51) presented with an ICH or FND.

About a quarter of the cohort (*n* = 73, 27%) received interventional treatment (either surgical excision or stereotactic radiotherapy) during the total follow-up period available: of these, almost a half (*n* = 35, 48%) presented with a seizure, a third (*n* = 26, 36%) with an ICH, 10 (14%) with an FND, and 2 (3%) incidentally. Twenty adults (7.5%) had an ICH within five years of diagnosis: eleven (55%) had presented with an ICH, four each (20%) with a seizure or FND, and one adult incidentally.

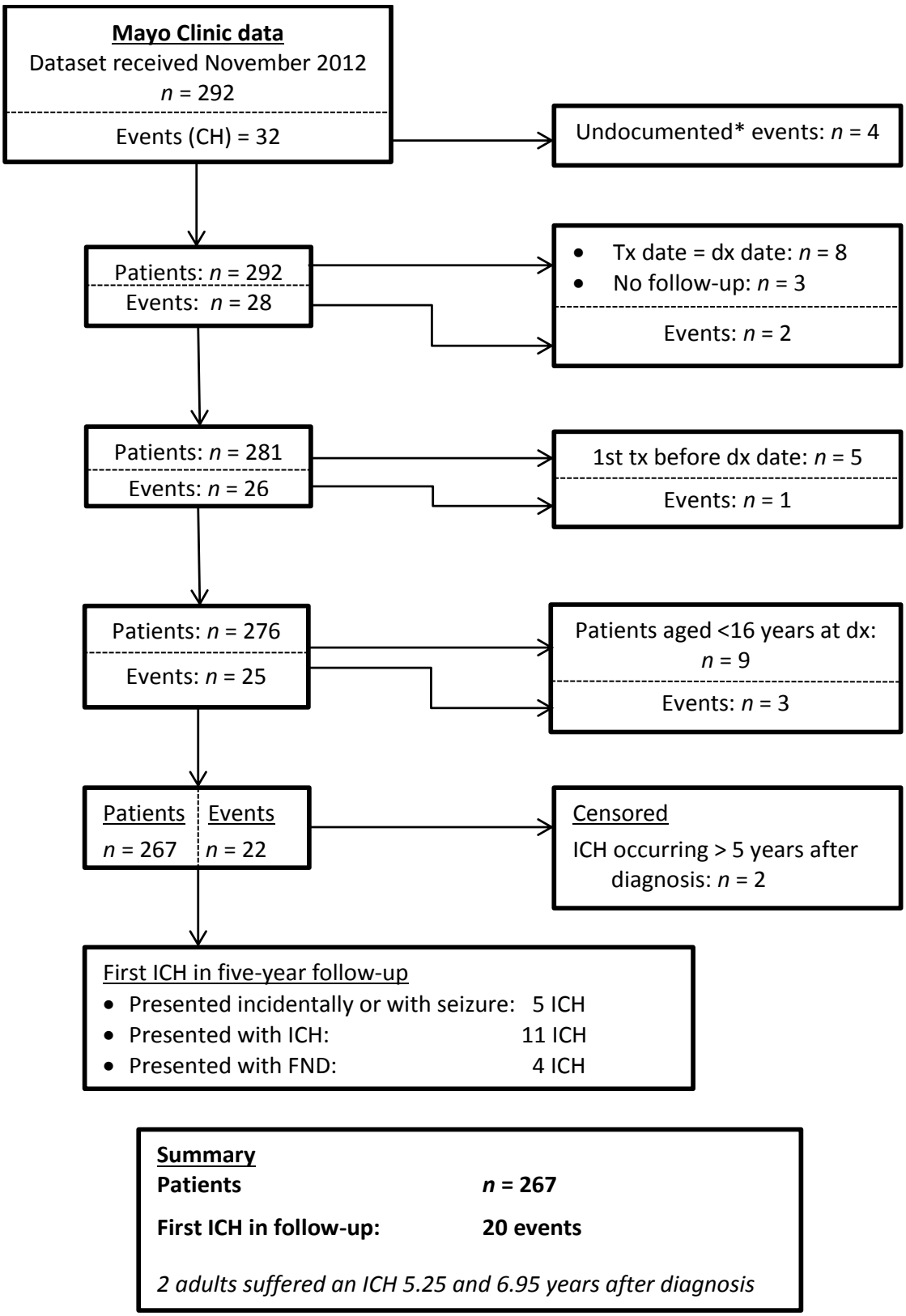



**Figure 7.2 Flowchart showing composition of cohort from Mayo Clinic, Rochester, MN**

**Table 7.3 Mayo Clinic cohort: baseline characteristics**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total *n* = 267 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (*n* = 98, 37%) | | Seizure (*n* = 76, 28%) | | ICH (*n* = 64, 24%) | | FND (*n* = 29, 11%) | | | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Age at diagnosis (median, IQR) | 55 | 34–69 | 40 | 29–52 | 44 | 29–56 | 50 | 40–67 | 46 | 31–62 |
| Sex | | | | | | | | | | |
| Male | 46 | 47% | 39 | 51% | 24 | 38% | 15 | 52% | 124 | 46% |
| Female | 52 | 53% | 37 | 49% | 40 | 63% | 14 | 48% | 143 | 54% |
| Primary CCM location | | | | | | | | | | |
| Lobar | 56 | 57% | 74 | 97% | 24 | 38% | 2 | 7% | 156 | 58% |
| Deep | 20 | 20% | 1 | 1% | 7 | 11% | 6 | 21% | 34 | 13% |
| Cerebellum | 11 | 11% | 0 | 0% | 2 | 3% | 1 | 3% | 14 | 5% |
| Brainstem | 11 | 11% | 1 | 1% | 31 | 48% | 20 | 69% | 63 | 24% |
| Single or multiple CCMs | | | | | | | | | | |
| Single | 85 | 87% | 61 | 80% | 50 | 78% | 22 | 76% | 218 | 82% |
| Multiple | 13 | 13% | 15 | 20% | 14 | 22% | 7 | 24% | 49 | 18% |
| Management* | | | | | | | | | | |
| Surgery/radiosurgery | 2 | 2% | 35 | 46% | 26 | 41% | 10 | 35% | 73 | 27% |
| Conservative management | 96 | 98% | 41 | 54% | 38 | 59% | 19 | 66% | 193 | 73% |
| 1st clinical event in follow-up | | | | | | | | | | |
| ICH | 1 | 1% | 4 | 5% | 11 | 17% | 4 | 14% | 20 | 7% |
| No event in follow-up | 97 | 99% | 72 | 95% | 53 | 83% | 25 | 86% | 247 | 93% |
| Length of censored follow-up (years) (median, IQR) | 5.0 | 1.9–5.0 | 3.9 | 1.1–5.0 | 2.7 | 0.4–5.0 | 5.0 | 0.8–5.0 | 4.5 | 1.1–5.0 |

*Management is over the entire follow-up period provided, not truncated at five years.

### 7.5.2 Toronto cohort

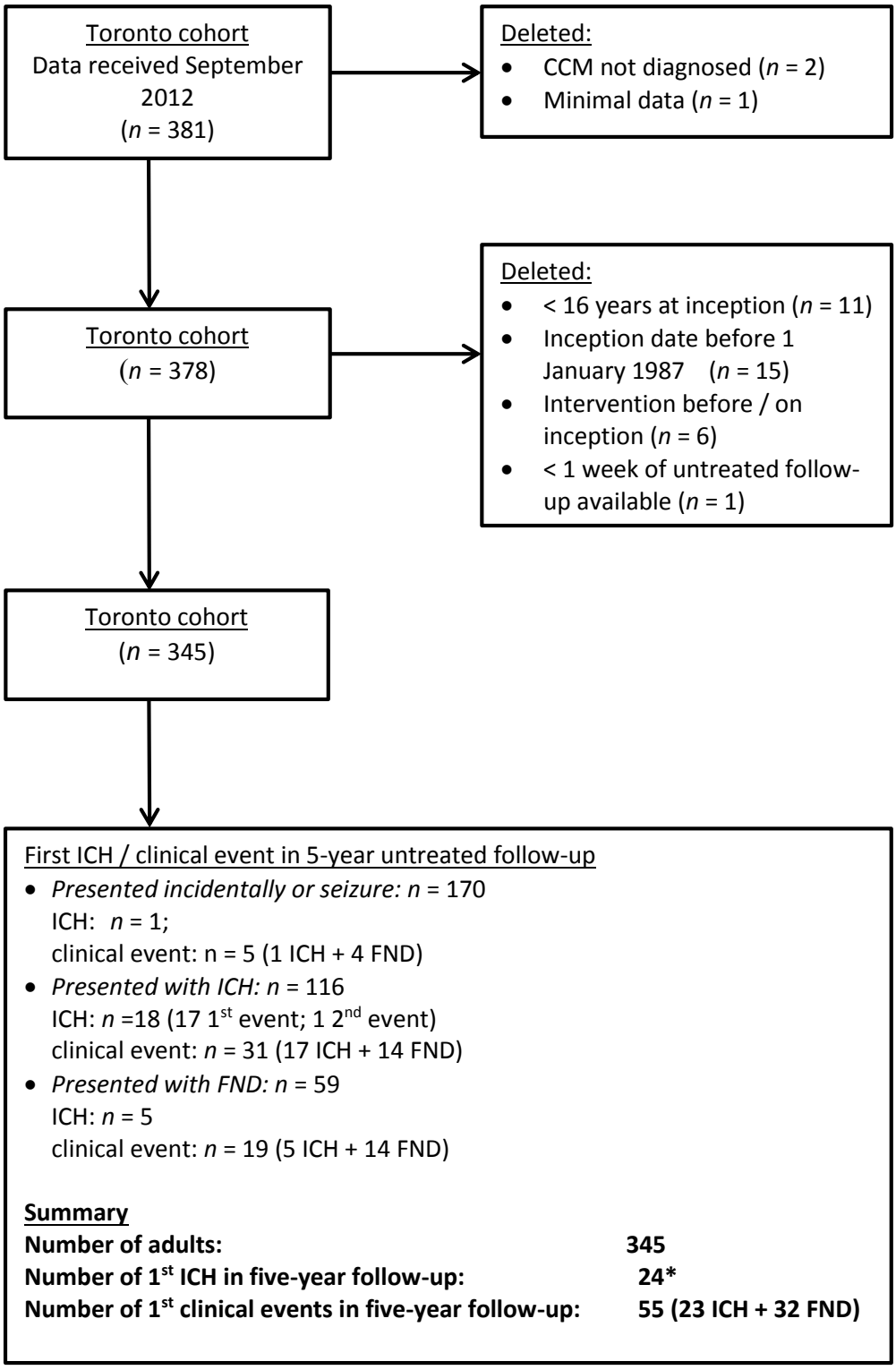
Between 1989 and 2008, some 569 patients with cavernous malformations attended a clinic at the Toronto Western Hospital; of these, however, only 381 individuals were reported to have both an initial assessment and a minimum of one year follow-up, and these patients formed the Toronto cohort in this study. In August 2012, a research clinician at Toronto Western Hospital searched the hospital electronic patient record system and the neuroradiology imaging database for follow-up for these 381 participants. Data pertaining to separate clinical events in follow-up were extracted onto a spreadsheet to ensure that the Toronto data were in a format compatible with other datasets in this meta-analysis.

During the data-cleaning process, a number of records were removed from the dataset (see the flowchart in Figure 7.3). In two cases, the diagnosis was not in fact CCM, and one record had minimal data; 11 people were diagnosed during childhood (aged less than 16 years); six adults received treatment on or before the date of diagnosis, and another less than a week after diagnosis; and fifteen individuals, who were diagnosed before 1 January 1987, had uncertain diagnosis dates ($n$ = 8) or were diagnosed between 1976 and 1986 ($n$ = 4), or the data seemed unreliable (for example, no notes in EPR and no imaging available) ($n$ = 3). After these records were deleted, the cohort from Toronto Western Hospital consisted of 345 adults, who experienced 24 haemorrhages within five years of follow-up, and 55 clinical events (23 ICH and 32 FND).

The baseline characteristics of this cohort are presented in Table 7.4 below. For approximately half of the cohort, the symptoms that led directly to CCM diagnosis were either ICH ($n$ = 116, 34%) or FND ($n$ = 59, 17%); a fifth of the cohort presented with a seizure ($n$ = 69, 20%) and the remainder incidentally ($n$ = 101, 29%). This cohort consisted of more women ($n$ = 194, 56%), and the median age at diagnosis was 42 years (interquartile range 33–54 years), which ranged from 36 years for those presenting with a seizure to 46 years for those presenting incidentally. There was a larger percentage of people with multiple lesions in the Toronto cohort ($n$ = 79, 23%)

than in the cohort from the Mayo Clinic (18%). Again, the percentage of adults with primary brainstem lesions was greater in the Toronto cohort ($n$ = 102, 30%) than in the Mayo Clinic (24%): 84 (82%) of those with a brainstem lesion presented with either an ICH or FND, and 14 people with a brainstem lesion presented incidentally.

A smaller percentage of the Toronto cohort received interventional treatment ($n$ = 40, 12%) over the course of the entire follow-up period, compared with the Mayo Clinic cohort (27%), and of these, 31 (78%) presented with an ICH or FND. Among the 24 people who experienced a first haemorrhage within five years of diagnosis, 18 (75%) presented with an ICH and 5 (21%) presented with FND; among those who suffered an FND in the first five years of follow-up ($n$ = 32), 14 each (44%) presented with ICH or FND, and 4 (12%) presented incidentally or with a seizure.




**One adult experienced an ICH as a second event, having suffered an FND earlier in follow-up.*

**Figure 7.3 Flowchart showing composition of final Toronto cohort**

**Table 7.4 Toronto cohort: baseline characteristics**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total *n* = 345 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (*n* = 101, 29%) | | Seizure (*n* = 69, 20%) | | ICH (*n* = 116, 34%) | | FND (*n* = 59, 17%) | | | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Age at diagnosis (median, IQR) | 46 | 35–55 | 36 | 27–48 | 40 | 34–52 | 44 | 34–57 | 42 | 33–54 |
| Sex | | | | | | | | | | |
| Male | 39 | 39% | 35 | 51% | 48 | 41% | 29 | 49% | 151 | 44% |
| Female | 62 | 61% | 34 | 49% | 68 | 59% | 30 | 51% | 194 | 56% |
| Primary CCM location | | | | | | | | | | |
| Lobar | 67 | 66% | 62 | 90% | 44 | 38% | 16 | 27% | 189 | 55% |
| Deep | 9 | 9% | 2 | 3% | 13 | 11% | 6 | 10% | 30 | 9% |
| Cerebellum | 11 | 11% | 1 | 1% | 7 | 6% | 5 | 9% | 24 | 7% |
| Brainstem | 14 | 14% | 4 | 6% | 52 | 45% | 32 | 54% | 102 | 30% |
| Single or multiple CCMs | | | | | | | | | | |
| Single | 80 | 79% | 52 | 75% | 91 | 78% | 43 | 73% | 266 | 77% |
| Multiple | 21 | 21% | 17 | 25% | 25 | 22% | 16 | 27% | 79 | 23% |
| Management* | | | | | | | | | | |
| Surgery/radiosurgery | 1 | 1% | 8 | 12% | 25 | 22% | 6 | 10% | 40 | 12% |
| Conservative management | 100 | 99% | 61 | 88% | 91 | 78% | 53 | 90% | 305 | 88% |
| 1st clinical event in 5-year follow-up | 3 | 3% | 2 | 3% | 31 | 27% | 19 | 32% | 55 | 16% |
| 1st ICH | 0 | 0% | 1 | 1% | 18* | 16% | 5 | 9% | 24† | 7% |
| 1st FND | 3 | 3% | 1 | 1% | 14 | 12% | 14 | 24% | 32 | 9% |
| 1st clinical event in total follow-up | 3 | 3% | 2 | 3% | 40 | 35% | 24 | 41% | 69 | 20% |
| Length of follow-up (median, IQR) | 3.4 | 1.8–5.0 | 4.7 | 2.1–5.0 | 2.6 | 1.2–4.5 | 4.3 | 1.5–5.0 | 3.2 | 1.5–5.0 |

*Management is over the entire follow-up period provided, not truncated at five years.

†One adult experienced an ICH as a second event, having had an FND earlier in follow-up.

### 7.5.3 Cohort from Hôpital Lariboisière, Paris

The initial datafile from Hôpital Lariboisière contained 104 patients, but 23 records were removed because of minimal data available (1), no follow-up (18), CCM was diagnosed in childhood (1), intervention on or before diagnosis (2), and diagnosed before 1 January 1987 (1). Hence the final cohort consisted of 81 adults, who had four haemorrhages within five years of diagnosis (see flowchart in Figure 7.4).

The baseline characteristics for this cohort are displayed in Table 7.5. More than half the adults presented incidentally ($n$ = 47, 58%); of the remainder, 14 (17%) presented with an FND, and equal numbers with seizure and haemorrhage ($n$ = 10, 12%). The cohort consists of more women ($n$ = 47, 58%) than men, and the percentage of adults with multiple lesions is larger than in the other cohorts ($n$ = 27, 33%). The comparatively large number of adults who harbour multiple lesions is unsurprising, since much of the research in identifying genes responsible for the familial form of the disease, which is characterized by the presence of multiple lesions, has been conducted in a unit attached to Hôpital Lariboisière.

The median age at diagnosis is 42 years (interquartile range 28–59 years), ranging from a median of 35 years for those presenting with an ICH to 49 years for those presenting incidentally. Seventeen patients (21%) have brainstem lesions: of these, 8 (47%) presented incidentally and 9 with either ICH or FND. Four patients received interventional treatment for their lesion (two presenting incidentally and two with an ICH). The median length of follow-up for this cohort is 2.2 years (interquartile range 0.7–4.2), which is shorter than that for the other cohorts.

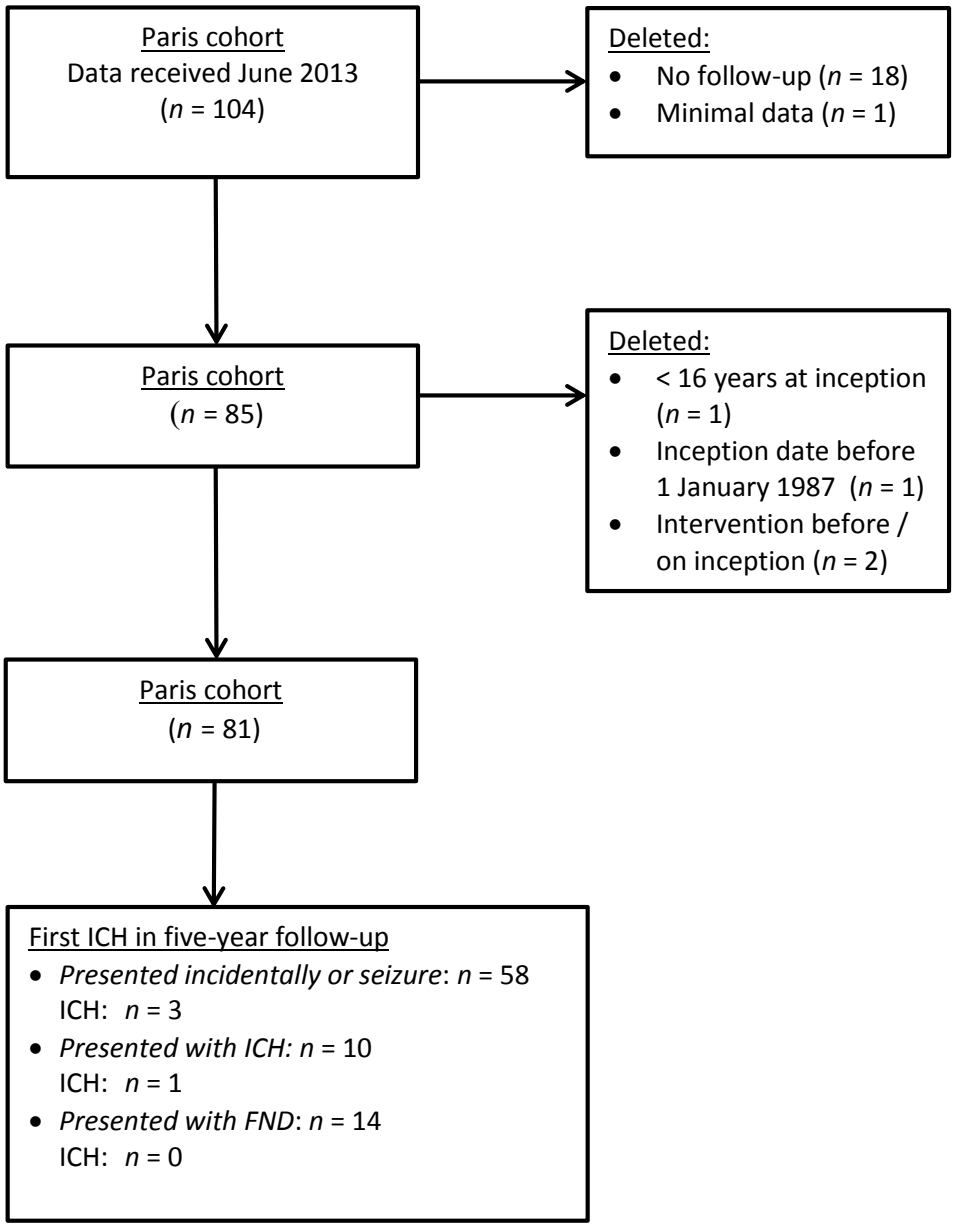



**Figure 7.4 Flowchart showing composition of cohort from Hôpital Lariboisière, Paris**

**Table 7.5 Paris cohort: baseline characteristics**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total *n* = 81 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (*n* = 47, 58%) | | Seizure (*n* = 10, 12%) | | ICH (*n* = 10, 12%) | | FND (*n* = 14, 17%) | | | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Age at diagnosis (median, IQR) | 49 | 29–61 | 41 | 25–59 | 35 | 23–42 | 40 | 34–63 | 42 | 28–59 |
| Sex | | | | | | | | | | |
| Male | 20 | 43% | 5 | 50% | 4 | 40% | 5 | 36% | 34 | 42% |
| Female | 27 | 57% | 5 | 50% | 6 | 60% | 9 | 64% | 47 | 58% |
| CCM location | | | | | | | | | | |
| Brainstem | 8 | 17% | – | – | 6 | 60% | 3 | 21% | 17 | 21% |
| Other location | 39 | 83% | 10 | 100% | 4 | 40% | 11 | 79% | 64 | 79% |
| Single or multiple CCMs | | | | | | | | | | |
| Single | 28 | 60% | 8 | 80% | 8 | 80% | 10 | 71% | 54 | 67% |
| Multiple | 19 | 40% | 2 | 20% | 2 | 20% | 4 | 29% | 27 | 33% |
| Management* | | | | | | | | | | |
| Surgery/radiosurgery | 2 | 4% | – | 0% | 2 | 20% | – | – | 4 | 5% |
| Conservative management | 45 | 96% | 10 | 100% | 8 | 80% | 14 | 100% | 77 | 95% |
| 1st clinical event in follow-up | | | | | | | | | | |
| ICH | 3 | 6% | – | – | 1 | 10% | – | – | 4 | 5% |
| No event in follow-up | 44 | 94% | 10 | 100% | 9 | 90% | 14 | 100% | 77 | 95% |
| Length of censored follow-up (years) (median, IQR) | 2.2 | 1.0–4.0 | 2.0 | 0.4–3.7 | 2.0 | 0.4–4.0 | 2.2 | 0.5–4.9 | 2.2 | 0.7–4.2 |

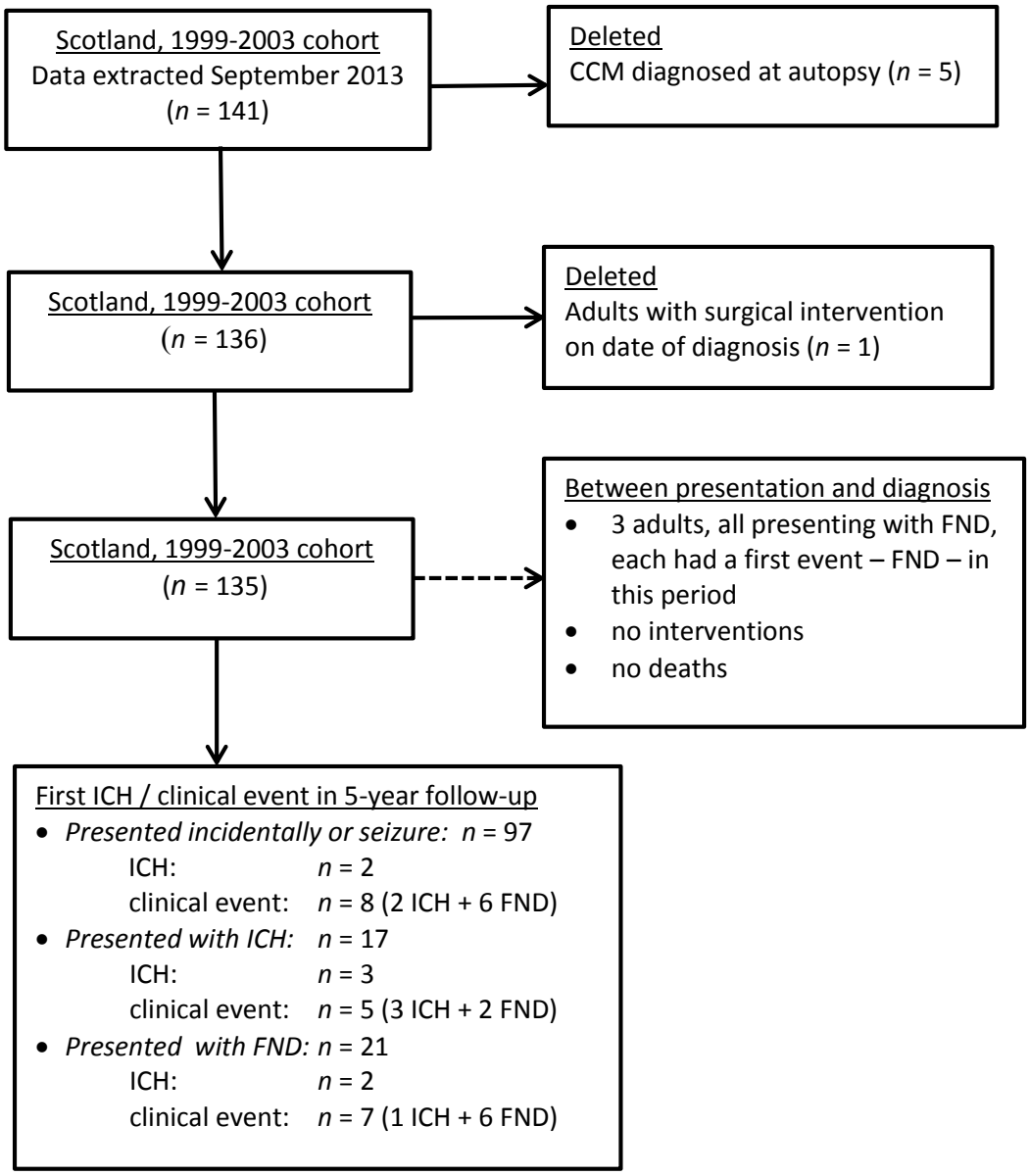
*Management is over the entire follow-up period provided, not truncated at five years.

### 7.5.4 First Scottish cohort

Figure 7.5 displays the flowchart for this cohort, with inception now changed to date of diagnosis. In the five-year period between 1999 and 2003, 141 residents in Scotland (aged 16 years or over), received a first-ever CCM diagnosis, validated by magnetic resonance imaging (MRI) or pathological examination. Five adults were diagnosed at autopsy, and another was diagnosed after their lesion had been surgically excised.

Between presentation and diagnosis, three adults in this cohort, all of whom presented with FND, each suffered a recurrent FND; however, as follow-up in this study starts at time of diagnosis, these events are not included in the analysis, but merely reported for information. Similarly, outcome events that occur more than five years after diagnosis are excluded from analysis; in this cohort there is only one occurrence: an adult who presented incidentally, but suffered her first FND 11.5 years after diagnosis, and then a recurrent FND nine months later. Therefore the earlier Scottish cohort consists of 135 adults, seven of whom had a first ICH within five years of diagnosis, and twenty had a first clinical event (six ICH and fourteen FND).

The baseline characteristics for this cohort are displayed in Table 7.6. Of 135 adults in the cohort, almost half presented incidentally ($n$ = 62, 46%), a quarter with a seizure ($n$ = 35, 26%), 17 (13%) with a haemorrhage, and 21 (16%) with an FND. There are 80 women (59%) in the cohort, and the median age at diagnosis was 41 years (interquartile range 32–53 years), ranging from a median of 34 years for those who presented with a seizure to 46 years for those presenting incidentally. In this cohort, 24 individuals (18%) had multiple lesions; only 17 adults (13%) had a primary brainstem lesion, and of these eight (47%) presented with an FND, four (24%) with an ICH, and 5 (29%) incidentally. Of the 23 who received surgical intervention, 10 (43%) presented with seizure. Seven people had a first ICH within five years of diagnosis (two each presenting incidentally or with an FND, three with an ICH); twenty suffered a first clinical event in the same period (one presented with a seizure, five an ICH, and seven each with FND or incidentally).




***Summary***

**Participants** ***n* = 135**

**Events in 5 years of follow-up**

**First ICH in follow-up:** **7 ICH** (1 fatal)
**First clinical event in follow-up:** **20 events** **(6 ICH + 14 FND)**

*Events between presentation and diagnosis*
*3 adults had an FND*

*Events more than 5 years after diagnosis*
*1 adult presenting incidentally: 1st FND 11.5 years after diagnosis; 2nd FND 0.75 years later*

**Figure 7.5 Flowchart showing composition of first Scottish cohort**

**Table 7.6 Scotland, 1999–2003: baseline characteristics**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total *n* = 135 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (*n* = 62, 46%) | | Seizure (*n* = 35, 26%) | | ICH (*n* = 17, 13%) | | FND (*n* = 21, 16%) | | | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Age at diagnosis (median, IQR) | 46 | 34–56 | 34 | 26–46 | 35 | 29–46 | 42 | 33–62 | 41 | 32–53 |
| Sex | | | | | | | | | | |
| Male | 23 | 37% | 21 | 60% | 5 | 29% | 6 | 29% | 55 | 41% |
| Female | 39 | 63% | 14 | 40% | 12 | 71% | 15 | 71% | 80 | 59% |
| Primary CCM location | | | | | | | | | | |
| Lobar | 43 | 69% | 35 | 100% | 7 | 41% | 5 | 24% | 90 | 67% |
| Deep | 4 | 7% | 0 | 0% | 1 | 6% | 4 | 19% | 9 | 7% |
| Cerebellum | 10 | 16% | 0 | 0% | 5 | 29% | 4 | 19% | 19 | 14% |
| Brainstem | 5 | 8% | 0 | 0% | 4 | 24% | 8 | 38% | 17 | 13% |
| Single or multiple CCMs | | | | | | | | | | |
| Single | 56 | 90% | 23 | 66% | 14 | 82% | 18 | 86% | 111 | 82% |
| Multiple | 6 | 10% | 12 | 34% | 3 | 18% | 3 | 14% | 24 | 18% |
| Management* | | | | | | | | | | |
| Surgery/radiosurgery | 5 | 8% | 10 | 29% | 6 | 35% | 2 | 10% | 23 | 17% |
| Conservative management | 57 | 92% | 25 | 71% | 11 | 65% | 19 | 90% | 112 | 83% |
| 1st clinical event in follow-up | | | | | | | | | | |
| 1st ICH | 2 | 3% | 0 | 0% | 3 | 18% | 2† | 10% | 7† | 5% |
| 1st FND | 5 | 8% | 1 | 3% | 2 | 12% | 6 | 29% | 14 | 10% |
| No event in 5-year follow-up | 55 | 89% | 34 | 97% | 12 | 71% | 14 | 67% | 115 | 85% |
| Length of censored follow-up (years) (median, IQR) | 5.0 | 5.0–5.0 | 5.0 | 1.1–5.0 | 1.9 | 0.3–5.0 | 5.0 | 0.9–5.0 | 5.0 | 1.4–5.0 |

*Management is over entire follow-up period provided, not truncated at five years.
†One adult experienced an ICH as a second event, having had an FND earlier in follow-up

### 7.5.5 Second Scottish cohort

In the five-year period between 2006 and 2010, 166 adults resident in Scotland received a first-ever CCM diagnosis, which was validated by MRI or pathological examination (see flowchart in Figure 7.6). One adult was diagnosed at autopsy, and five others were removed from the datafile, as their lesions were discovered after surgical excision: thus the second Scottish cohort consists of 160 adults, who had a total of seven ICH and six FND within five years of diagnosis.

Baseline characteristics are given in Table 7.7 below. In contrast to the earlier Scottish cohort, in the later one men ($n$ = 83, 52%) slightly outnumbered women ($n$ = 77, 48%), and the median age at diagnosis was five years older, at 46 years (interquartile range 34–60 years), ranging from 38 years for people presenting with seizures to 58 for those with FND. A quarter of the cohort presented with either ICH ($n$ = 31, 19%) or FND ($n$ = 10, 6%), a third ($n$ = 52, 33%) with seizure, and the remainder incidentally ($n$ = 67, 42%). Nearly a fifth ($n$ = 29, 18%) harboured multiple lesions, and a sixth ($n$ = 25, 16%) had primary brainstem lesions, 17 (68%) of whom presented with either an ICH or FND, and 7 (28%) incidentally. Only 11 (7%) patients had received interventional treatment for their lesions during the total follow-up period available, but this figure is probably artificially low because of the short length of follow-up for many individuals in this cohort (see section 7.3 above, and subsection 4.3.1 in Chapter 4). Of the thirteen adults who suffered a clinical event, ten (77%) experienced an initial ICH or FND which led subsequently to CCM diagnosis.

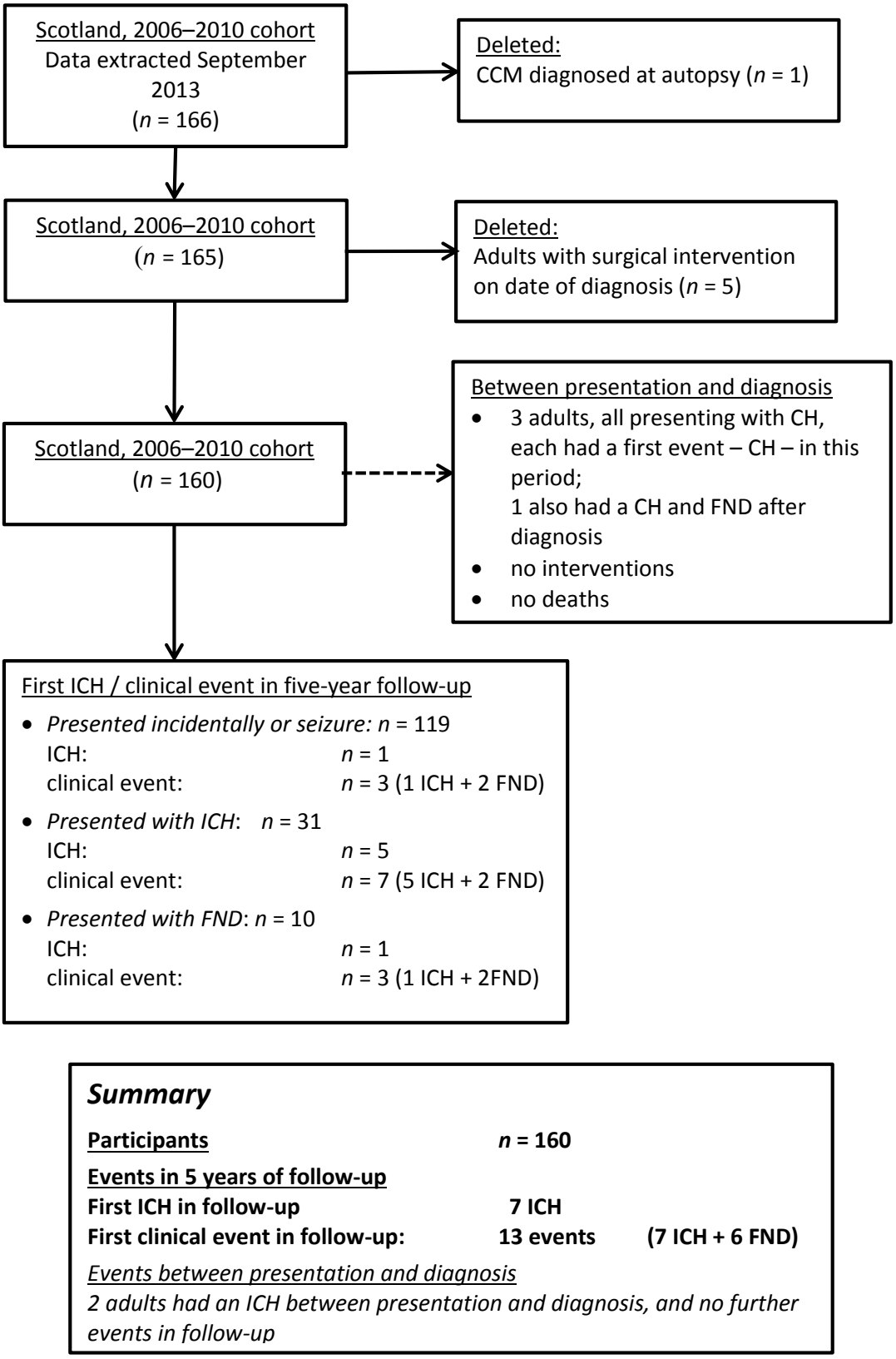



**Figure 7.6 Flowchart showing composition of second Scottish cohort**

**Table 7.7 Second Scottish cohort: baseline characteristics**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total *n* = 160 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (*n* = 67, 42%) | | Seizure (*n* = 52, 33%) | | ICH (*n* = 31, 19%) | | FND (*n* = 10, 6%) | | | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Age at diagnosis (median, IQR) | 54 | 43–63 | 38 | 29–52 | 44 | 32–60 | 58 | 52–61 | 46 | 34–60 |
| Sex | | | | | | | | | | |
| Male | 31 | 46% | 32 | 62% | 16 | 52% | 4 | 40% | 83 | 52% |
| Female | 36 | 54% | 20 | 39% | 15 | 48% | 6 | 60% | 77 | 48% |
| Primary CCM location | | | | | | | | | | |
| Lobar | 51 | 76% | 51 | 98% | 15 | 48% | 3 | 30% | 120 | 75% |
| Deep | 1 | 2% | 0 | 0% | 3 | 10% | 0 | 0% | 4 | 3% |
| Cerebellum | 8 | 12% | 0 | 0% | 2 | 7% | 1 | 10% | 11 | 7% |
| Brainstem | 7 | 10% | 1 | 2% | 11 | 36% | 6 | 60% | 25 | 16% |
| Single or multiple CCMs | | | | | | | | | | |
| Single | 57 | 85% | 43 | 83% | 22 | 71% | 9 | 90% | 131 | 82% |
| Multiple | 10 | 15% | 9 | 17% | 9 | 29% | 1 | 10% | 29 | 18% |
| Management* | | | | | | | | | | |
| Surgery/radiosurgery | 2 | 3% | 3 | 6% | 6 | 19% | 0 | 0% | 11 | 7% |
| Conservative management | 65 | 97% | 49 | 94% | 25 | 81% | 10 | 100% | 149 | 93% |
| 1st clinical event in follow-up | | | | | | | | | | |
| ICH | 0 | 0% | 1 | 2% | 5 | 16% | 1 | 10% | 7 | 4% |
| FND | 1 | 2% | 1 | 2% | 2 | 7% | 2 | 20% | 6 | 4% |
| No event in follow-up | 66 | 99% | 50 | 96% | 24 | 77% | 7 | 70% | 147 | 92% |
| Length of censored follow-up (years) (median, IQR) | 3.6 | 2.9–4.9 | 4.1 | 2.9–5.0 | 3.0 | 1.8–4.1 | 3.5 | 2.5–5.0 | 3.9 | 2.9–5.0 |

*Management is over the entire follow-up period provided, not truncated at five years.

# Chapter 8: Results of the individual patient data meta-analysis

## 8.1 Introduction

As described in the previous chapter, this individual patient data meta-analysis comprises five cohorts, with a total size of 988 adults. However, although all five studies recorded the number of intracranial haemorrhages experienced during follow-up, only three studies (the two Scottish cohorts and Toronto) recorded focal neurological deficits in follow-up, and therefore the number of adults in the analysis of the outcome 'clinical event' was 640. If the six highly selected cohorts that were originally invited to join the collaboration are excluded (see Table 7.1 above), the present study ($n$ = 988) includes 65% of the more general potential cases that were previously identified.

The flowcharts for each individual study (Figures 7.2–7.6 above) illustrate how the final number of participants was achieved for each cohort; this is summarized for the entire study in Figure 8.1 below. In the hospital-based cohorts, 292 adults were diagnosed with a cerebral cavernous malformation between March 1984 and August 1998, and 267 people were eligible to form the Mayo Clinic cohort; 381 adults were diagnosed between 1 January 1987 and mid-December 2007, and 345 form the Toronto Western Hospital cohort; and of 104 individuals diagnosed between August 1994 and August 2011, 81 adults are included in the Paris cohort. Patients did not necessarily receive a first diagnosis at these three institutions; however, if they were diagnosed elsewhere, then they were referred subsequently to one of these three institutions, either as out- or inpatients.

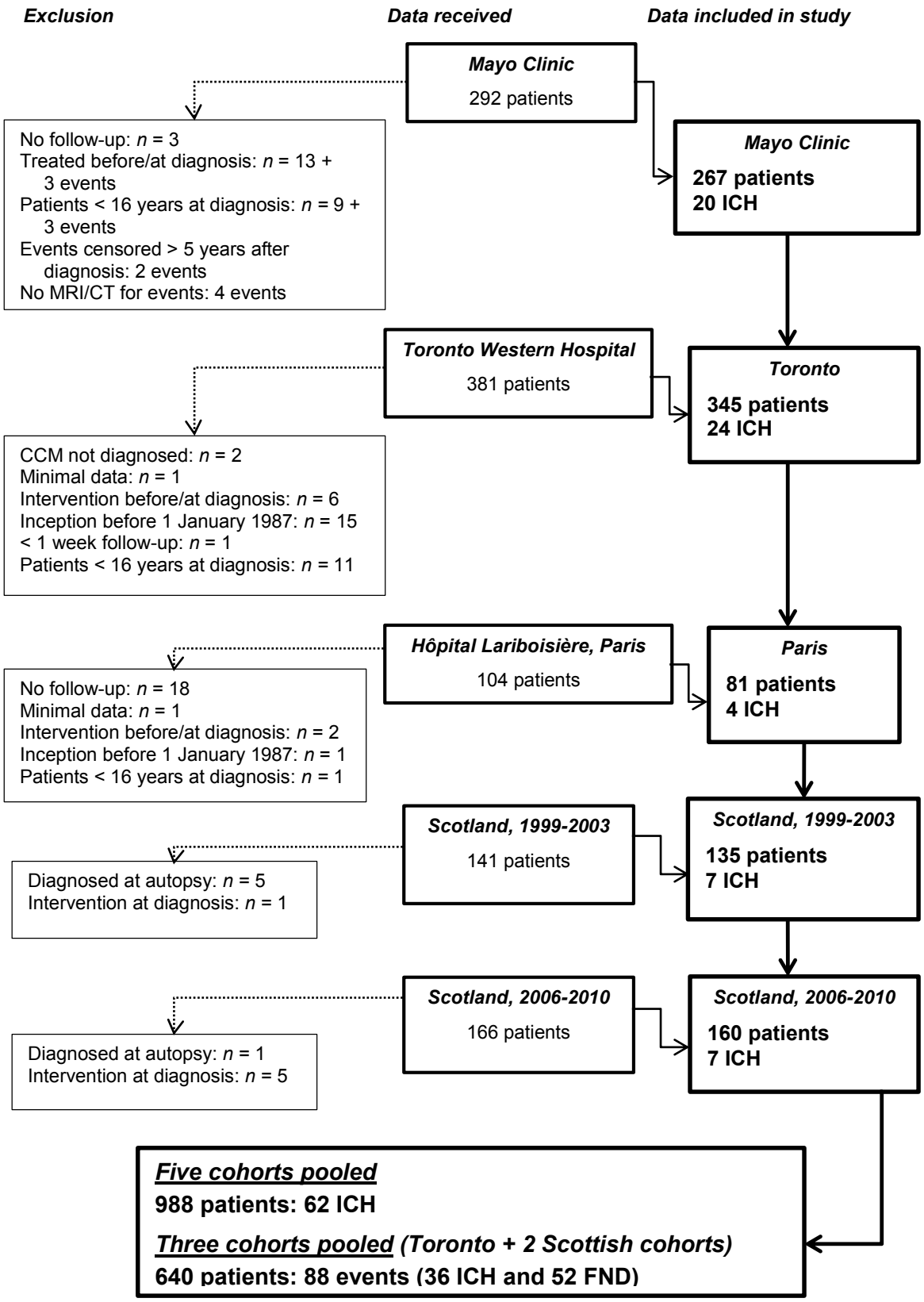



**Figure 8.1 Flowchart showing composition of cohorts included in the study**

By contrast, in a prospective population-based study within two five-year time-spans in a single country – Scotland – 135 adults were alive at the time of receiving a first-ever CCM diagnosis between 1999 and 2003, and had not undergone interventional treatment for their lesion at the time of diagnosis, and similarly 160 adults between 2006 and 2010. Although these two cohorts originated from the same population, the decision was taken to analyse them separately. (The rationale behind this decision was discussed in section 7.3 of Chapter 7 above.)

Therefore this individual patient data meta-analysis includes 693 participants from three hospital-based studies located in three different countries, and 295 adults from two cohorts of a nationwide population-based study that were recruited over two different periods of time.

### Follow-up in the second Scottish cohort

Between 2006 and 2010, 160 adults resident in Scotland were diagnosed with a cerebral cavernous malformation: of these, thirteen had a clinical event within five years of diagnosis; twelve were censored at the time of interventional treatment, if they had not experienced a prior clinical event; and six died within five years of diagnosis (a seventh died in the sixth year).

The remaining participants in the cohort ($n = 129$) were censored at last contact or five years after diagnosis, whichever occurred first. For this subsection of the cohort, the length of follow-up available ranged from a minimum of 1.75 years to a maximum of 7.5, with forty adults (31%) having the full five-year period and 30 (23%) having between 1.75 and 3 years; the median length of follow-up was 4 years (interquartile range 3.0 to 5.6 years) (see Figure 8.2).

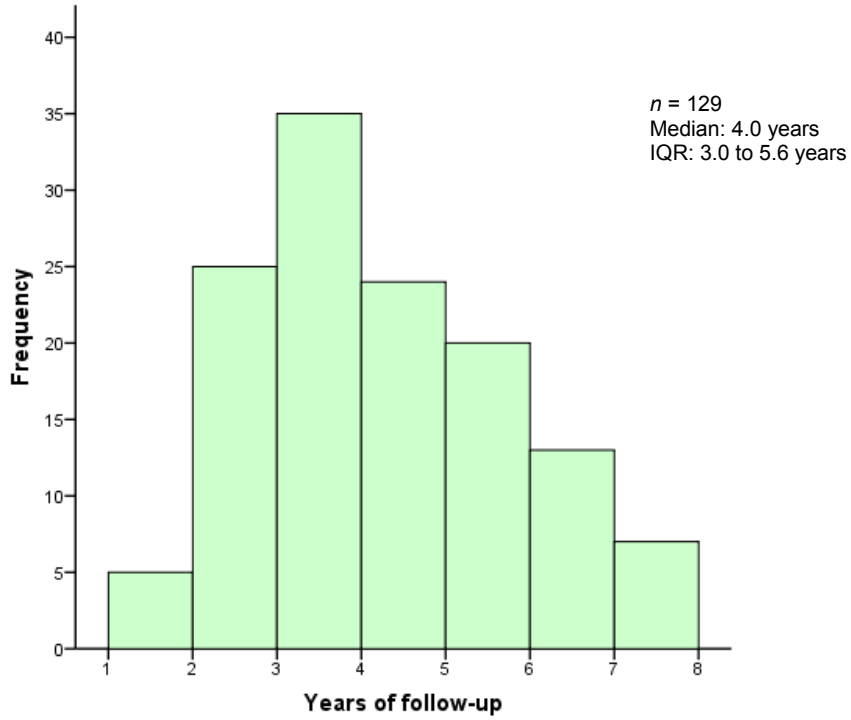



**Figure 8.2 Follow-up for adults censored at last contact in second Scottish cohort**

## 8.2 Baseline characteristics

Baseline characteristics for each individual cohort, stratified by mode of clinical presentation, were presented in Chapter 7 (Tables 7.3–7.7). In this chapter, the baseline characteristics of the five-cohort and three-cohort pooled studies are displayed in Table 8.1(a) and (b) respectively, and graphs of the five pre-specified predictors, grouped by study, are presented in Figures 8.3–8.7.

In Table 8.2, the composition of the five cohorts and the two pooled studies is examined: percentages are presented to enable a comparison of the distribution of baseline characteristics in each individual cohort, together with the median age and length of untreated follow-up available.

**Table 8.1 Pooled cohorts: baseline characteristics, interventions and first clinical events, stratified by mode of presentation**

**(a) Intracranial haemorrhage analysis (five pooled cohorts)**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total *n* = 988 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (*n* = 375, 38%) | | Seizure (*n* = 242, 25%) | | ICH (*n* = 238, 24%) | | FND (*n* = 133, 14%) | | | |
| | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** |
| Age at diagnosis (median, IQR) | 50 | 36-61 | 38 | 27-50 | 40 | 32-53 | 48 | 36-61 | 44 | 32-57 |
| Sex | | | | | | | | | | |
| Male | 159 | 42% | 132 | 55% | 97 | 41% | 59 | 44% | 447 | 45% |
| Female | 216 | 58% | 110 | 46% | 141 | 59% | 74 | 56% | 541 | 55% |
| Primary CCM location | | | | | | | | | | |
| Lobar | 256 | 68% | 232 | 96% | 94 | 40% | 37 | 28% | 619 | 63% |
| Deep | 34 | 9% | 3 | 1% | 24 | 10% | 16 | 12% | 77 | 8% |
| Cerebellum | 40 | 11% | 1 | 0.4% | 16 | 7% | 11 | 8% | 68 | 7% |
| Brainstem | 45 | 12% | 6 | 3% | 104 | 44% | 69 | 52% | 224 | 23% |
| CCM multiplicity | | | | | | | | | | |
| Single | 306 | 82% | 187 | 77% | 185 | 78% | 102 | 77% | 780 | 79% |
| Multiple | 69 | 18% | 55 | 23% | 53 | 22% | 31 | 23% | 208 | 21% |
| Management (w/in 5 years of diagnosis) | | | | | | | | | | |
| Surgery/radiosurgery | 9 | 2% | 47 | 19% | 43 | 18% | 8 | 6% | 107 | 11% |
| Conservative management | 366 | 98% | 195 | 81% | 195 | 82% | 125 | 94% | 881 | 89% |
| 1st clinical event in follow-up | 6 | 2% | 6 | 3% | 38 | 16% | 12 | 9% | 62 | 6% |
| Length of censored follow-up (years) (median, IQR) | 4.2 | 2.0-5.0 | 4.6 | 1.8-5.0 | 2.7 | 0.7-5.0 | 4.5 | 1.4-5.0 | 3.9 | 1.5-5.0 |

**Table 8.1** ***contd***

**(b) Clinical event (ICH or FND) analysis (three pooled cohorts)**

| Characteristic | Type of symptom leading to CCM diagnosis | | | | | | | | Total *n* = 640 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Incidental (*n* = 230, 36%) | | Seizure (*n* = 156, 24%) | | ICH (*n* = 164, 26%) | | FND (*n* = 90, 14%) | | | |
| | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** |
| Age at diagnosis (median, IQR) | 48 | 37-58 | 36 | 27-48 | 40 | 33-53 | 48 | 35-59 | 43 | 33-56 |
| Sex | | | | | | | | | | |
| Male | 93 | 40% | 88 | 56% | 69 | 42% | 39 | 43% | 289 | 45% |
| Female | 137 | 60% | 68 | 44% | 95 | 58% | 51 | 57% | 351 | 55% |
| Primary CCM location | | | | | | | | | | |
| Lobar | 161 | 70% | 148 | 95% | 66 | 40% | 24 | 27% | 399 | 62% |
| Deep | 14 | 6% | 2 | 1% | 17 | 10% | 10 | 11% | 43 | 7% |
| Cerebellum | 29 | 13% | 1 | 1% | 14 | 9% | 10 | 11% | 54 | 8% |
| Brainstem | 26 | 11% | 5 | 3% | 67 | 41% | 46 | 51% | 144 | 23% |
| CCM multiplicity | | | | | | | | | | |
| Single | 193 | 84% | 118 | 76% | 127 | 77% | 70 | 78% | 508 | 79% |
| Multiple | 37 | 16% | 38 | 24% | 37 | 23% | 20 | 22% | 132 | 21% |
| 1st clinical event in 5-yr follow-up | 11 | 5% | 5 | 3% | 43 | 26% | 29 | 32% | 88 | 14% |
| ICH | 2 | 1% | 2 | 1% | 25 | 15% | 7 | 8% | 36 | 6% |
| FND | 9 | 4% | 3 | 2% | 18 | 11% | 22 | 24% | 52 | 8% |
| Length of censored follow-up (years) (median, IQR) | 4.2 | 2.4-5.0 | 4.8 | 2.2-5.0 | 2.6 | 1.1-4.4 | 4.3 | 1.5-5.0 | 3.9 | 1.9-5.0 |

**Table 8.2 Comparison of composition of five cohorts and pooled studies: baseline characteristics (percentages)**

| Cohort | Age (years) | | Sex | | Presentation | | | | Brainstem | Multiplicity | | Follow-up (years) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | median | IQR | Male | Female | Incidental | Seizure | ICH | FND | | Single | Multiple | median | IQR |
| **Mayo Clinic** | 46 | 31–62 | 46 | 54 | 37 | 29 | 24 | 11 | 24 | 82 | 18 | 4.5 | 1.1–5.0 |
| **Toronto** | 42 | 33–54 | 44 | 56 | 29 | 20 | 34 | 17 | 30 | 77 | 23 | 3.2 | 1.5–5.0 |
| **Paris** | 42 | 28–59 | 42 | 58 | 58 | 12 | 12 | 17 | 21 | 67 | 33 | 2.2 | 0.7–4.2 |
| **Scotland, 1999-2003** | 41 | 32–53 | 41 | 59 | 46 | 26 | 13 | 16 | 13 | 82 | 18 | 5.0 | 1.4–5.0 |
| **Scotland, 2006-2010** | 46 | 34–60 | 52 | 48 | 42 | 33 | 19 | 6 | 16 | 82 | 18 | 3.9 | 2.9–5.0 |
| **Total:** | | | | | | | | | | | | | |
| **5 cohorts** | 44 | 32–57 | 45 | 55 | 38 | 25 | 24 | 14 | 23 | 79 | 21 | 3.9 | 1.5–5.0 |
| **3 cohorts** | 43 | 33–56 | 45 | 55 | 36 | 24 | 26 | 14 | 23 | 79 | 21 | 3.9 | 1.9–5.0 |

**Note**: All figures in columns sex, presentation, brainstem and multiplicity are percentages.

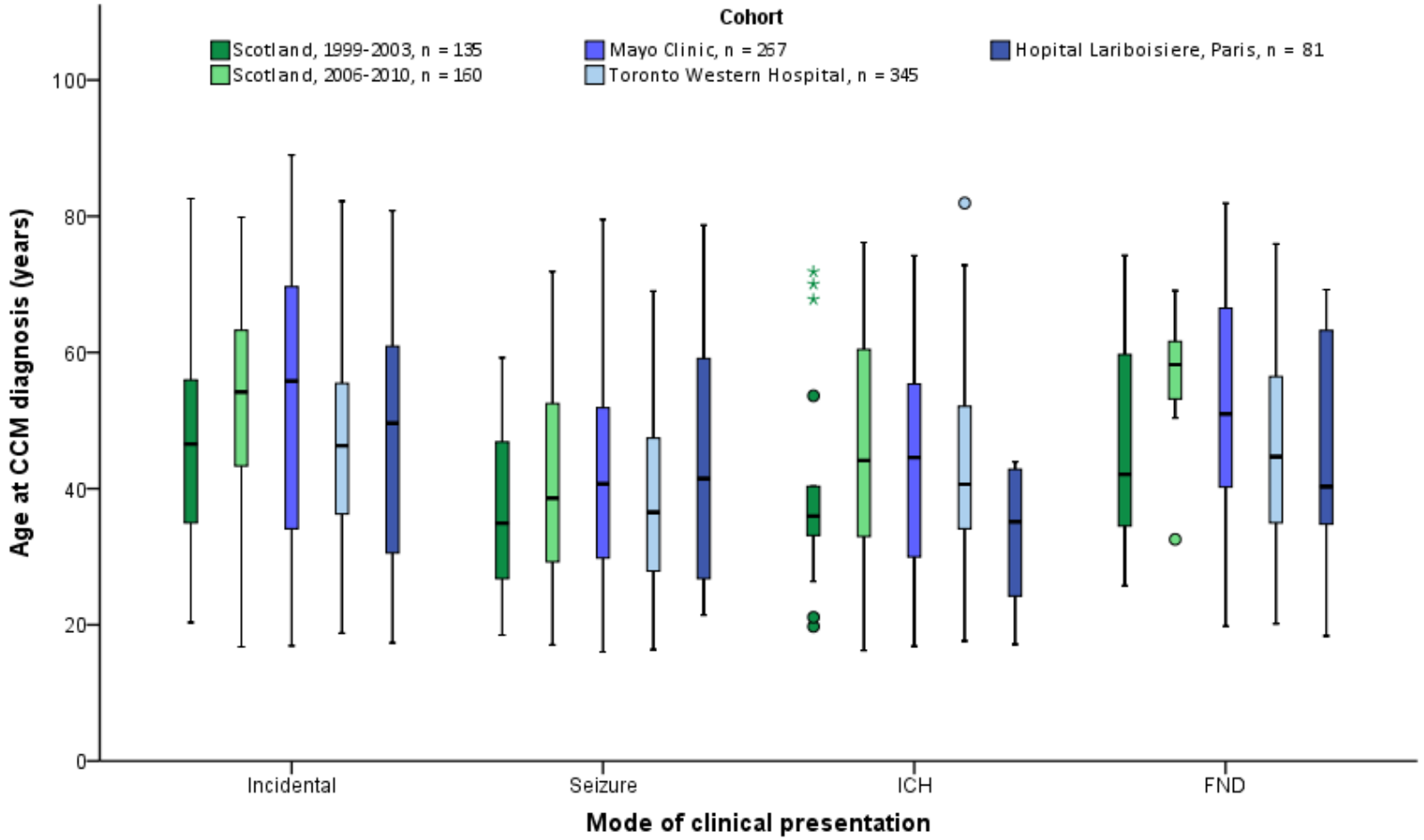



**Figure 8.3 Boxplot of age at diagnosis, by mode of presentation, stratified by study**

Median age for the entire study is 44 years (interquartile range 32 to 57 years), ranging from 38 years for seizure presentation to 50 years for incidental presentation (see Table 8.1(a)). Comparing individual cohorts (Table 8.2), median age ranges from 41 years (Scotland, 1999–2003) to 46 years (Scotland, 2006–2010 and Mayo Clinic).

There is a slight predominance of women ($n$ = 541, 55%), both in total and in ICH, FND and incidental presentations, but this trend is reversed in seizure presentation, where the number of men is 132 (55%). Among the individual cohorts, the percentage of women ranges from 48% (Scotland, 2006–2010) to 59% (Scotland, 1999–2003).

With regard to mode of clinical presentation, a quarter presented with intracranial haemorrhage ($n$ = 238, 24%) and seizure ($n$ = 242, 25%), 133 with focal neurological deficit (14%), and 375 (38%) incidentally. The percentage presenting incidentally ranged from 29% (Toronto) to 58% (Paris), with seizure from 12% (Paris) to 33% (the later Scottish cohort), with ICH from 12% (Paris) to 34% (Toronto), and with FND from 6% (the later Scottish cohort) to 17% (both Toronto and Paris).

Almost a quarter of the pooled cohort had a primary brainstem cavernous malformation ($n$ = 224, 23%), 77% of whom ($n$ = 173) presented with ICH or FND. In the individual cohorts, brainstem location ranged from 13% (Scotland, 1999–2003) to 30% (Toronto). About a fifth of the entire study had multiple lesions ($n$ = 208, 21%); this ranged from 18% (Scotland, both cohorts and Mayo Clinic) to 33% (Paris). Hôpital Lariboisière is a national reference centre for rare neurovascular diseases of the eye and brain, and also specializes in research on the genetic form of the disease, in which form individuals tend to have multiple CCM; therefore it is of little surprise that the Paris cohort has a large percentage of multiple lesions.

The median length of censored follow-up available for the entire study was 3.9 years (interquartile range 1.5 to 5.0 years); the median length for those presenting with ICH was 2.7 years, but the other presentations had medians of at least 4 years. Median follow-up varied from 2.2 years (Paris) to 5 years (first Scottish cohort).

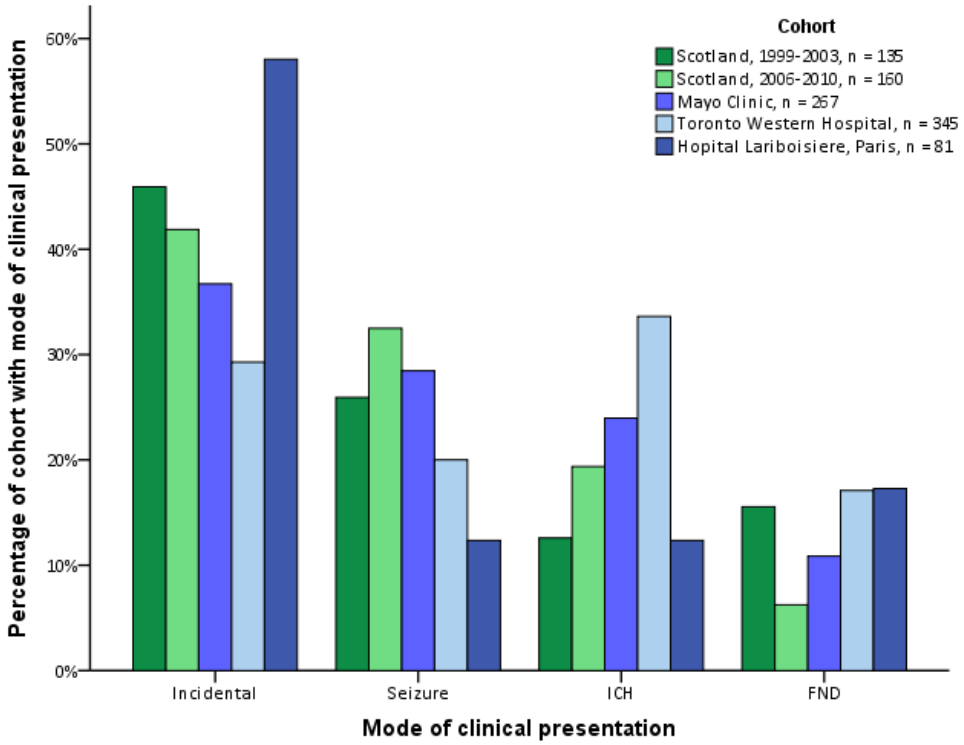



**Figure 8.4 Frequency distribution of mode of clinical presentation, stratified by study**

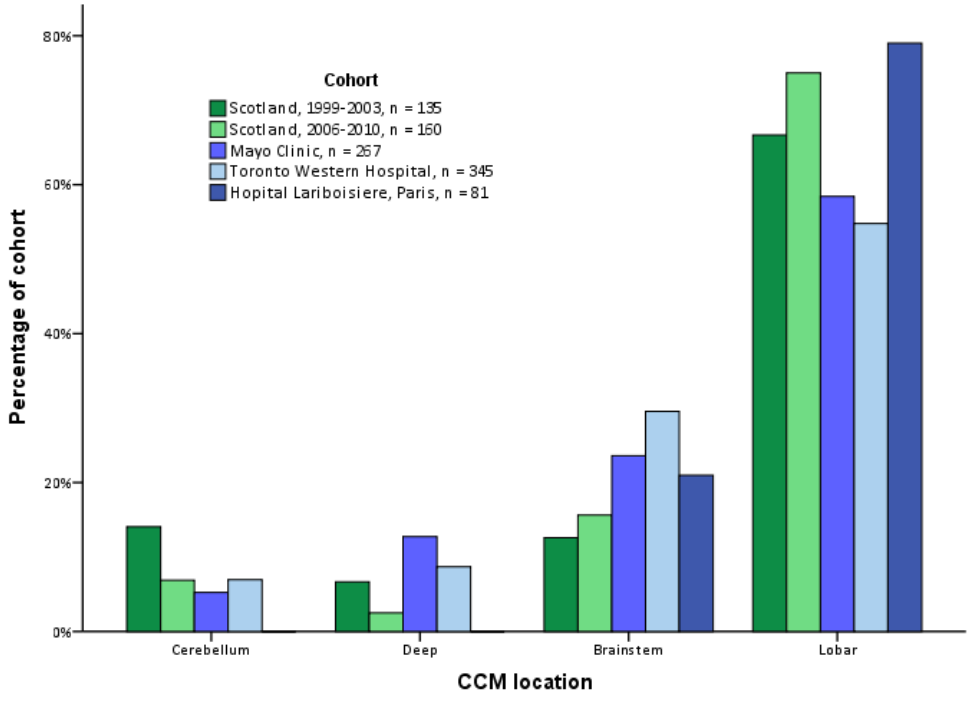



**Figure 8.5 Frequency distribution of CCM location, stratified by study**

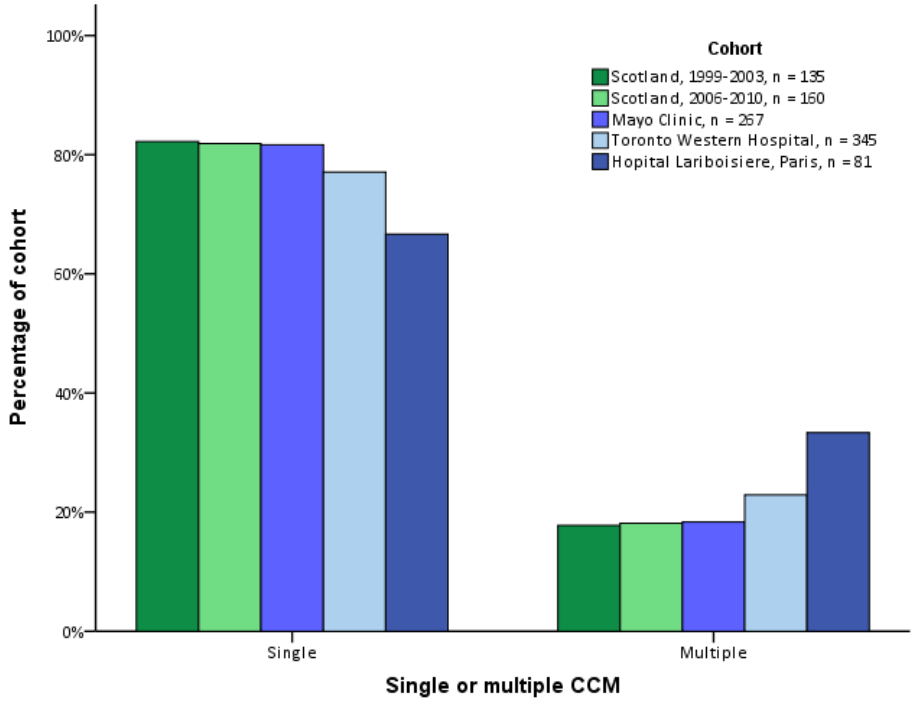



**Figure 8.6 Frequency distribution of CCM multiplicity, stratified by study**

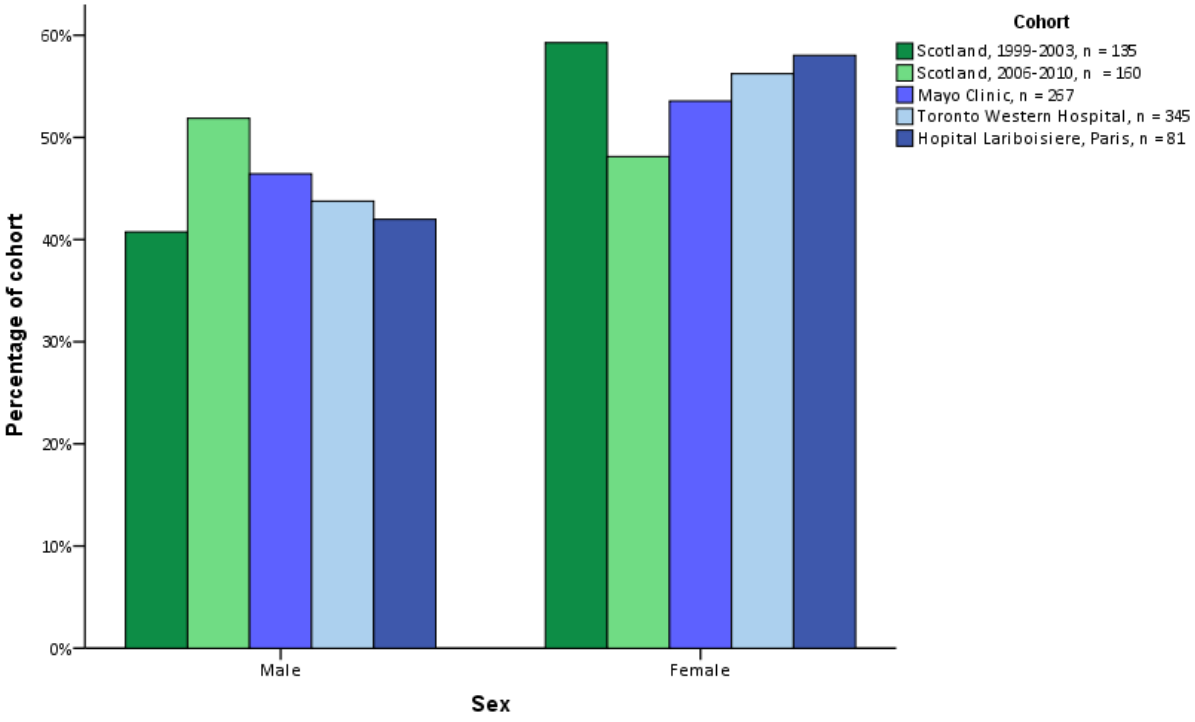



**Figure 8.7 Frequency distribution of sex, stratified by study**

## 8.3 Censoring at interventional treatment

In this study, patients who had not suffered a previous haemorrhage or FND during follow-up were censored at first treatment date, if they underwent interventional treatment – whether surgical excision or stereotactic radiotherapy – for their CCM. To investigate the possibility of informative censoring, as described in Chapter 6 above, follow-up of those participants who were censored for treatment has been explored in greater depth.

In the pooled cohort, 157 participants (16%) received some form of interventional treatment for their cavernoma: however, 37 had treatment after experiencing at least one clinical event within five years of diagnosis, and 13 had treatment more than five years after diagnosis (see Figure 8.8). The remaining 107 participants (11%) were censored for interventional treatment during the five-year follow-up period; of these 47 presented with epilepsy and 60 presented with an intracranial haemorrhage, focal neurological deficit or incidentally. The percentage of each cohort censored for treatment (within five years of CCM diagnosis) ranged from 4.6% (Toronto) to 21% (Mayo Clinic) (see Table 8.5 below).

A breakdown of the length of follow-up available before interventional treatment, stratified by mode of presentation, is shown in Table 8.3. Of those censored for treatment during the five-year follow-up period, 92 (86%) had less than two years of follow-up: 63 (59%) had less than six months' follow-up, and 14 (13%) had between six months and a year.

Informative censoring is less of a potential problem for patients who present with a seizure and subsequently undergo interventional treatment than for those who are treated after a non-seizure presentation, since the decision for surgery with a seizure presentation is predominantly informed by intractable epilepsy rather than by the risk of future intracranial haemorrhage.

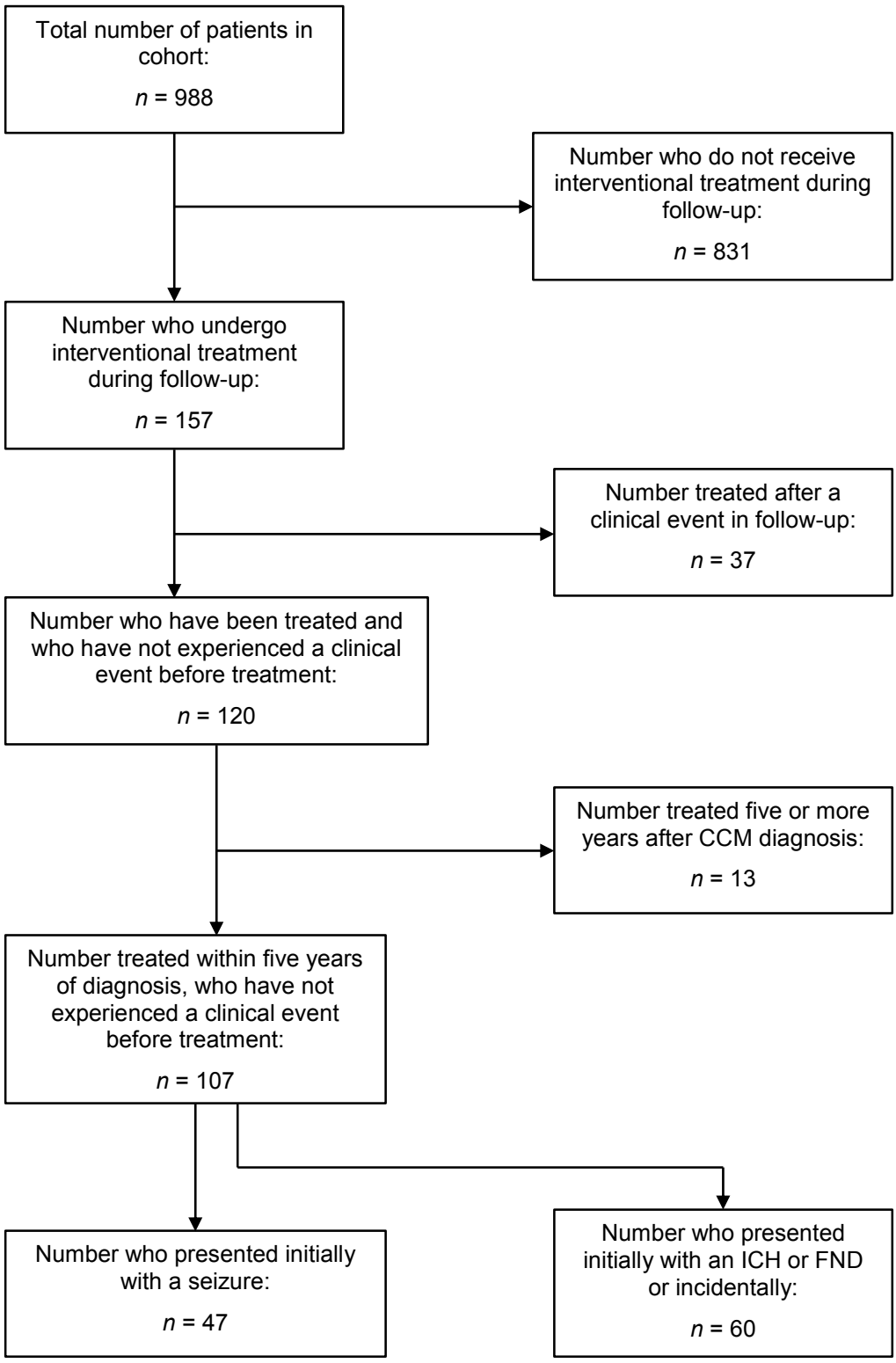



**Figure 8.8 Flowchart of those receiving interventional treatment**

**Table 8.3 Length of follow-up before treatment, stratified by mode of presentation**

| Mode of presentation | Length of follow-up (years) | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | < 0.5 | 0.5–0.99 | 1–1.99 | 2–2.99 | 3–3.99 | 4–4.99 | |
| **Seizure** | 20 | 5 | 12 | 4 | 2 | 4 | 47 |
| **Incidental** | 7 | 1 | 0 | 1 | 0 | 0 | 9 |
| **ICH** | 32 | 6 | 3 | 2 | 0 | 0 | 43 |
| **FND** | 4 | 2 | 0 | 0 | 0 | 2 | 8 |
| **Total** | 63 | 14 | 15 | 7 | 2 | 6 | 107 |

Cells contain number of adults.

Participants whose data are most likely to be affected by competing risks and therefore prone to informative censoring are those who presented initially with an ICH or FND and have less than two years of follow-up; these 47 participants form 4.8% of the entire study (see Table 8.3). After re-examining the five datafiles for any indication of a reason for interventional treatment, it would appear that 51 participants had treatment related to epilepsy, 33 to ICH or FND, and 23 for undisclosed reasons (see Table 9.2).

In Table 8.4, baseline characteristics and length of follow-up are presented for participants who were treated within five years of diagnosis and with no prior clinical event occurring since diagnosis, and for the adults in the remainder of the study; the two groups are further subdivided by whether or not they initially presented with a seizure. Those who presented with a seizure tended to be younger than those with other presentations, but those who received interventional treatment were significantly younger than those who did not (Mann Whitney test, $p < 0.0001$). In both treatment groups, slightly more men presented with a seizure, and the overall sex ratio was similar in both groups. In addition, lesion location and multiplicity were similar in both treatment groups.

**Table 8.4 Comparison of treated and untreated groups, stratified by seizure and non-seizure presentation**

| Characteristic | | Treated* | | | Untreated† | | |
|---|---|---|---|---|---|---|---|
| | | Presented with seizure *n* = 47 (44%) | Other presentation *n* = 60 (56%) | Total *n* = 107 | Presented with seizure *n* = 195 (22%) | Other presentation *n* = 686 (78%) | Total n = 881 |
| Age at diagnosis | median | 37.5 | 39.1 | 37.5 | 38.8 | 47.6 | 45.2 |
| | IQR | (30.3–47.1) | (29.3–46.2) | 29.8–46.8 | (27.5–51.8) | (35.0–60.7) | 33.3–58.9 |
| Sex | Male | 24 (51%) | 20 (33%) | 44 (41%) | 108 (55%) | 295 (43%) | 403 (46%) |
| | Female | 23 (49%) | 40 (67%) | 63 (59%) | 87 (45%) | 391 (57%) | 478 (54%) |
| Presentation | Incidental | – | 9 (15%) | 9 (8%) | – | 366 (53%) | 366 (42%) |
| | ICH or FND | – | 51 (85%) | 51 (48%) | – | 320 (47%) | 320 (36%) |
| CCM location | Brainstem | – | 20 (33%) | 20 (19%) | 6 (3%) | 198 (29%) | 204 (23%) |
| | Cerebellum | 1 (2%) | 7 (12%) | 8 (8%) | – | 60 (9%) | 60 (7%) |
| | Deep | – | 7 (12%) | 7 (7%) | 3 (2%) | 67 (10%) | 70 (8%) |
| | Lobar | 46 (98%) | 26 (43%) | 72 (67%) | 186 (95%) | 361 (53%) | 547 (62%) |
| CCM multiplicity | Single | 37 (79%) | 51 (85%) | 88 (82%) | 150 (77%) | 542 (79%) | 692 (79%) |
| | Multiple | 10 (21%) | 9 (15%) | 19 (18%) | 45 (23%) | 144 (21%) | 189 (22%) |
| Follow-up (yrs) | median | 0.7 | 0.3 | 0.3 | 5.0 | 4.1 | 4.4 |
| | IQR | (0.3–1.4) | (0.04–0.56) | 0.05–1.1 | (3.0–5.0) | (2.0–5.0) | 2.1–5.0 |

*Censored for interventional treatment within five years of diagnosis, no prior clinical event in follow-up.

†The remainder of the cohort not in the 'treated' group.

Mode of presentation differed significantly between treatment groups ($\chi^2$ (2) = 49.4, $p$ < 0.0001): greater percentages presented with (i) ICH or FND and (ii) seizure in the treated group (48% and 44% respectively) compared to the conservatively managed group (36% and 22%). Conversely, the percentage presenting incidentally was significantly greater in the untreated group (42% versus 8%). The median length of follow-up was greatly reduced in the treated group: 0.3 years compared to 4.4 years in the conservatively managed group (Mann Whitney test, $p$ < 0.0001).

## 8.4 Risk of ICH or FND in five-year follow-up

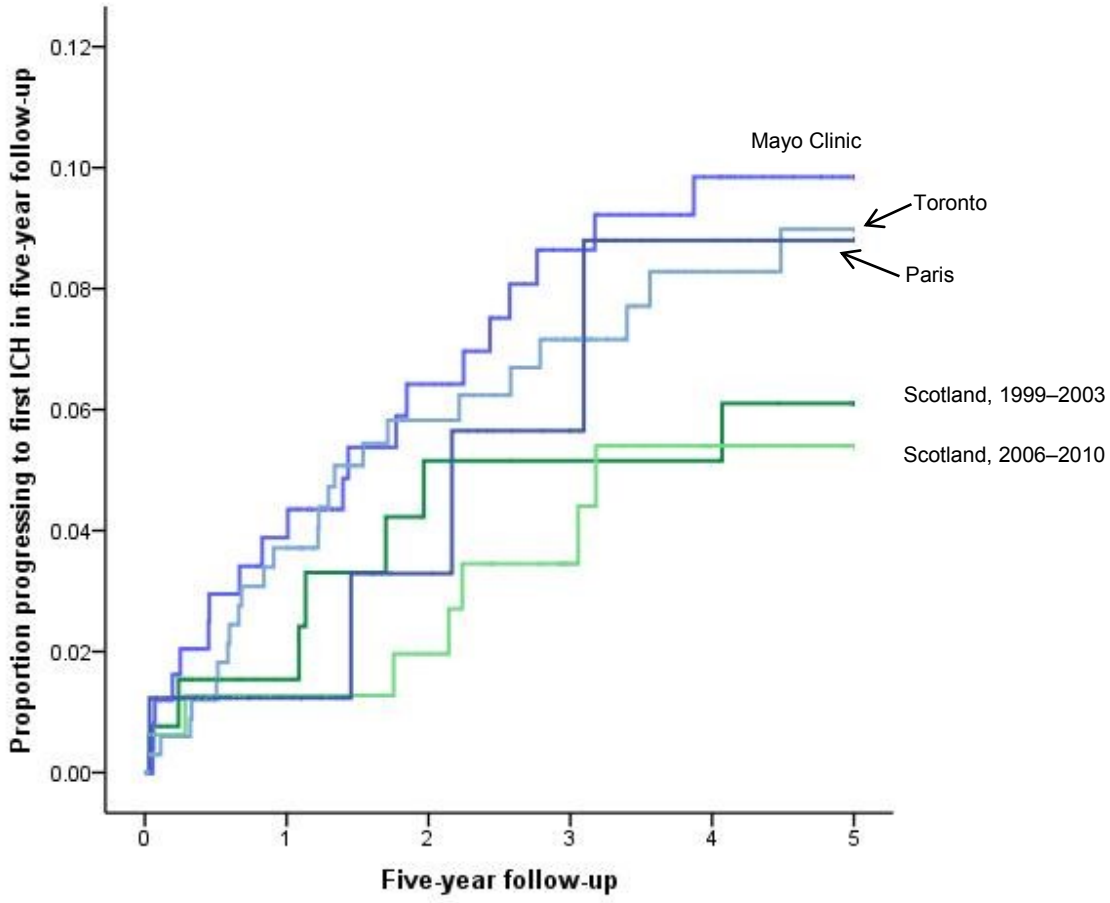
In the five-cohort analysis of risk of intracranial haemorrhage, 62 adults (6.3%) suffered a first ICH within five years of diagnosis – three of which were fatal – and in the three-cohort clinical-event analysis, 88 adults (13.8%) experienced either an ICH ($n$ = 36) or an FND ($n$ = 52). The contributions of each cohort to the two outcomes, together with the number who received interventional treatment within five years of diagnosis, are presented in Table 8.5. The number of haemorrhages in each cohort, as a percentage of its total population, was very similar and ranged from 4.4% (the later Scottish cohort) to 7.5% (Mayo Clinic).

To illustrate the distribution of outcome events among cohorts, Kaplan-Meier plots of the times to ICH and clinical event are presented in Figures 8.9 and 8.10. In Figure 8.9, the three hospital-based cohorts all have a greater cumulative risk of ICH over the five-year period than the two population-based cohorts; however, the scale of the $y$-axis has been magnified to enable the different cohort curves to be discerned more easily, and therefore the difference is not as great as might initially appear.

In Figure 8.10, progression to first haemorrhage or focal neurological deficit is very similar for the first Scottish cohort and the Toronto cohort, especially in the first three years, whereas the proportion of the second Scottish cohort who suffer a clinical event is smaller. This pattern is also apparent in Table 8.6, where the estimated risks of first haemorrhage (clinical event) in each cohort and for the pooled cohorts are presented: these range from 5.4% (second Scottish cohort) to 9.8% (Mayo Clinic).

**Table 8.5 Five cohorts: size, outcome events and number treated within five years of diagnosis**

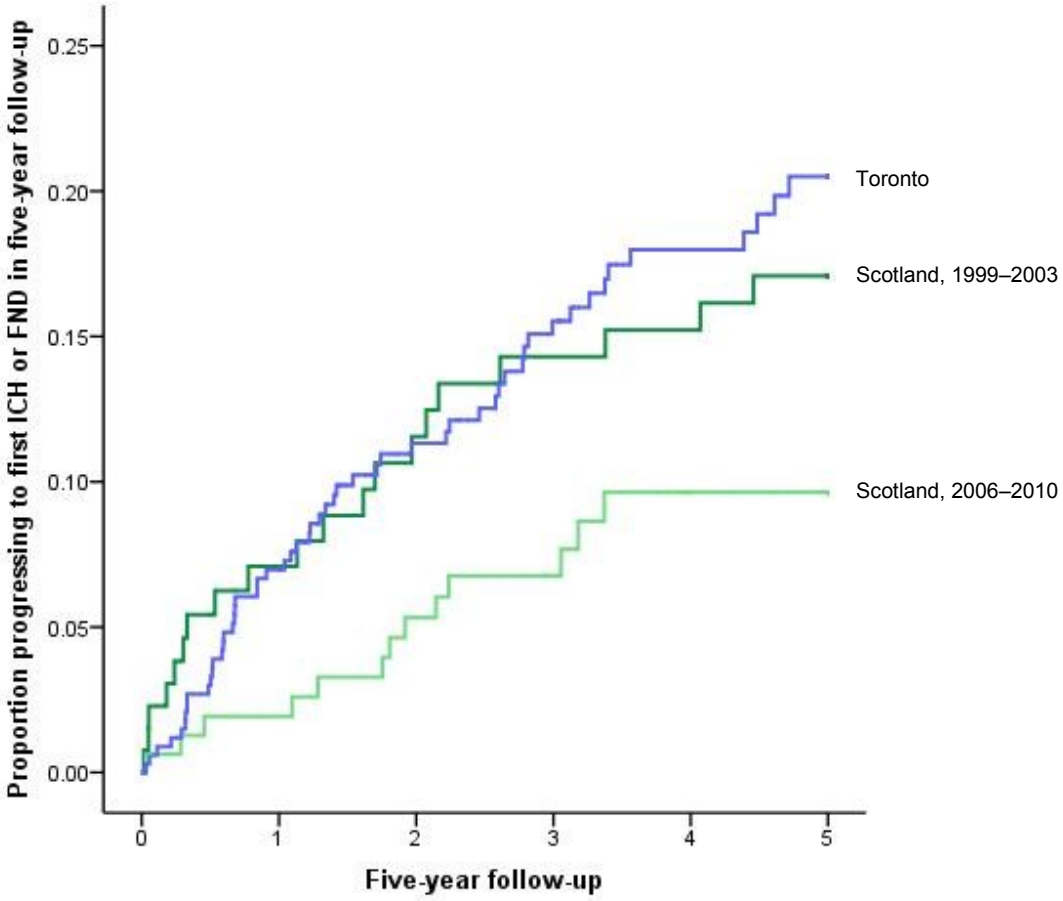
| Cohort | Adults | Treated | | 1st ICH (*n* = 988) | | 1st clinical event (*n* = 640) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | *%* | *n* | *%* | *n* | *%* | ICH | FND |
| **Mayo Clinic** | 267 | 56 | *21.0%* | 20 | *7.5%* | – | – | – | – |
| **Toronto** | 345 | 16 | *4.6%* | 24 | *7.0%* | 55 | *15.9%* | 23 | 32 |
| **Paris** | 81 | 4 | *4.9%* | 4 | *4.9%* | – | – | – | – |
| **Scotland, 1999–2003** | 135 | 19 | *14.1%* | 7 | *5.2%* | 20 | *14.8%* | 6 | 14 |
| **Scotland, 2006–2010** | 160 | 12 | *7.5%* | 7 | *4.4%* | 13 | *8.1%* | 7 | 6 |
| **Pooled cohorts:** | | | | | | | | | |
| **Five cohorts** | 988 | 107 | *10.8%* | 62 | *6.3%* | – | – | – | – |
| **Three cohorts** | 640 | 47 | *7.3%* | – | – | 88 | *13.8%* | 36 | 52 |




| Number of adults at risk (number of ICH in preceding year) | | | | | | |
|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | 135 | 113(2) | 102(4) | 101(0) | 101(0) | 97(1) |
| **Scotland, 2006–2010** | 160 | 145(2) | 135(1) | 105(2) | 66(2) | 40(0) |
| **Mayo Clinic** | 267 | 204(9) | 176(5) | 157(4) | 144(2) | 126(0) |
| **Toronto** | 345 | 301(12) | 238(6) | 189(3) | 144(2) | 120(1) |
| **Paris** | 81 | 57(1) | 42(1) | 33(1) | 22(1) | 14(0) |

***Note*** The scale of the *y*-axis has been magnified (proportion from 0 to 0.14 only) to enable the plots for each cohort to be inspected.

**Figure 8.9 Kaplan-Meier plot comparing estimated risk of first intracranial haemorrhage, stratified by study cohort**




**Number of adults at risk (number of clinical events in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | 135 | 109(9) | 97(5) | 93(3) | 92(1) | 88(2) |
| **Scotland, 2006–2010** | 160 | 145(3) | 135(5) | 105(2) | 66(3) | 40(0) |
| **Toronto** | 345 | 301(23) | 238(13) | 189(10) | 144(5) | 120(4) |

***Note*** The scale of the *y*-axis has been magnified (proportion from 0 to 0.24 only) to enable the plots for each cohort to be inspected.

**Figure 8.10 Kaplan-Meier plot comparing estimated risk of first clinical event (intracranial haemorrhage or focal neurological deficit), stratified by study cohort**

The Kaplan-Meier estimated risk of an intracranial haemorrhage (clinical event) in five-year follow-up has been calculated for the two core and three putative predictors; the risk is given for individual cohorts and for the pooled cohorts. For example, in Table 8.7, the Kaplan-Meier estimated risk of an ICH within five years of diagnosis for an adult presenting with an ICH or FND ranged from 4.2% (Paris) to 20.7% (Mayo Clinic), with a pooled-cohort estimated risk of 17.7% (95% confidence interval 13.1% to 22.3%), whereas the Kaplan-Meier estimated risk for an adult presenting with a seizure or incidentally ('other' presentation) varied from 0.6% (Toronto) to 10.8% (Paris), with the pooled-cohort estimated risk of 2.6% (95% CI 1.2% to 4.1%).

Similarly, in Table 8.8, the estimated risk of an ICH when the cavernous malformation is located in the brainstem ranged from 18.4% (Scotland, 1999–2003) to 34% (Scotland, 2006–2010), with a pooled-cohort risk of 21.1% (95% CI 14.9% to 27.2%), in contrast to the substantially lower risk when the CCM was located in another area of the brain (lowest: 0.8% in Scotland, 2006–2010; highest: 7.2% at Mayo Clinic; pooled-cohort estimate: 4.4%, 95% CI 2.6% to 6.1%). The tables for the other three putative predictors of haemorrhage and the five predictors of clinical event are located in Appendix F at the end of the thesis (see Tables A.1–A.8).

**Table 8.6 Kaplan-Meier estimated risk of haemorrhage and clinical event within five years of diagnosis, stratified by study**

| Cohort | Risk of ICH | | Risk of clinical event | |
|---|---|---|---|---|
| | Estimate | 95% CI | Estimate | 95% CI |
| **Mayo Clinic** | 9.8% | 5.7 to 14.0 | – | – |
| **Toronto** | 9.0% | 5.4 to 12.6 | 20.5% | 15.4 to 25.6 |
| **Paris** | 8.8% | 0.1 to 17.5 | – | – |
| **Scotland, 1999–2003** | 6.1% | 1.7 to 10.5 | 17.1% | 10.2 to 24.0 |
| **Scotland, 2006–2010** | 5.4% | 1.4 to 9.4 | 9.6% | 4.6 to 14.7 |
| **Pooled** | **8.1%** | **6.1 to 10.1** | **17.0** | **13.6 to 20.3** |

**Table 8.7 Estimated risk of intracranial haemorrhage within five years of CCM diagnosis, by initial presentation**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Mayo Clinic, Rochester, MN** | ICH/FND presentation | 93 | 15 | 20.7% | 11.2 to 30.1 | 0.048 |
| | Other presentation | 174 | 5 | 4.3% | 0.6 to 7.9 | 0.019 |
| **Toronto Western Hospital** | ICH/FND presentation | 175 | 23 | 17.7% | 10.8 to 24.6 | 0.035 |
| | Other presentation | 170 | 1 | 0.6% | 0 to 1.8 | 0.006 |
| **Hôpital Lariboisière, Paris** | ICH/FND presentation | 24 | 1 | 4.2% | 0 to 12.2 | 0.041 |
| | Other presentation | 57 | 3 | 10.8% | 0 to 22.6 | 0.060 |
| **Scotland, 1999-2003** | ICH/FND presentation | 38 | 5 | 15.9% | 3.0 to 28.8 | 0.066 |
| | Other presentation | 97 | 2 | 2.5% | 0 to 5.9 | 0.017 |
| **Scotland, 2006-2010** | ICH/FND presentation | 41 | 6 | 19.8% | 5.1 to 34.5 | 0.075 |
| | Other presentation | 119 | 1 | 0.9% | 0 to 2.7 | 0.009 |
| **Pooled cohorts** | ICH/FND presentation | 371 | 50 | 17.7% | 13.1 to 22.3 | 0.023 |
| | Other presentation | 617 | 12 | 2.6% | 1.2 to 4.1 | 0.008 |

**Table 8.8 Estimated risk of first intracranial haemorrhage within five years of CCM diagnosis, by lesion location**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Mayo Clinic, Rochester, MN** | Brainstem | 63 | 10 | 19.5% | 8.6 to 30.5 | 0.056 |
| | Other location | 204 | 10 | 7.2% | 2.9 to 11.5 | 0.022 |
| **Toronto Western Hospital** | Brainstem | 102 | 16 | 20.5% | 11.1 to 29.9 | 0.048 |
| | Other location | 243 | 8 | 4.5% | 1.3 to 7.6 | 0.016 |
| **Hôpital Lariboisière, Paris** | Brainstem | 17 | 3 | 25.1% | 0 to 50.8 | 0.131 |
| | Other location | 64 | 1 | 3.1% | 0 to 9.2 | 0.031 |
| **Scotland, 1999-2003** | Brainstem | 17 | 3 | 18.4% | 0 to 37.3 | 0.096 |
| | Other location | 118 | 4 | 4.2% | 0.1 to 8.2 | 0.020 |
| **Scotland, 2006-2010** | Brainstem | 25 | 6 | 34.0% | 10.4 to 57.7 | 0.121 |
| | Other location | 135 | 1 | 0.8% | 0 to 2.4 | 0.008 |
| **Pooled cohorts** | Brainstem | 224 | 38 | 21.1% | 14.9 to 27.2 | 0.031 |
| | Other location | 764 | 24 | 4.4% | 2.6 to 6.1 | 0.009 |

## 8.5 Univariate analysis

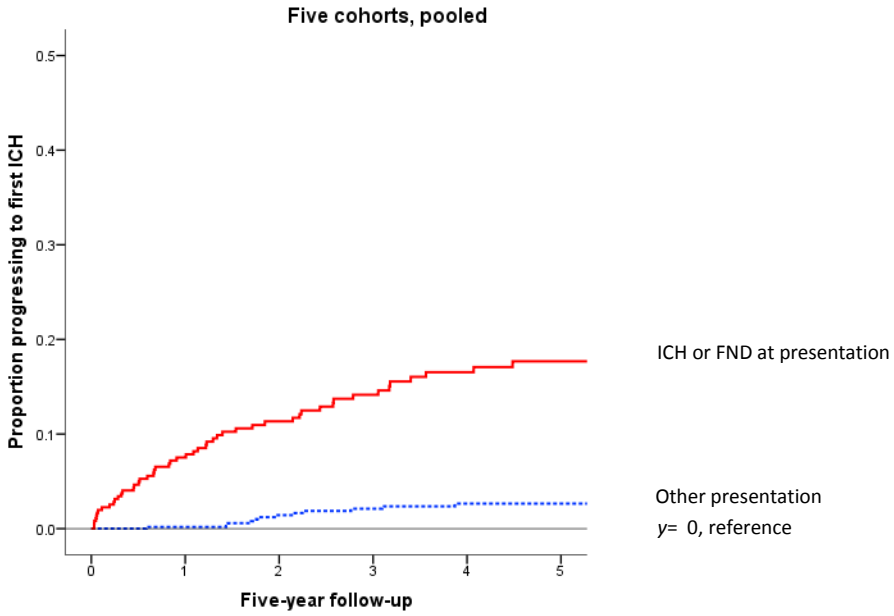
### 8.5.1 Kaplan-Meier plots

For each outcome event, five different Kaplan-Meier plots were produced, each plot stratified by a different *a priori* predictor in turn. Four plots comparing the estimated risk of first haemorrhage (clinical event), stratified by the two core predictors, for the pooled cohorts are displayed in Figures 8.11–8.12 below; plots for the individual cohorts, and also for the putative predictors, are presented in the Appendix G at the end of the thesis (Figures A.1–A.13). Age was categorized into three groups – 35 years or younger, 36–53 years, or 54 years or older – solely to enable a visual examination of the effect of different age-groups on the clinical outcome.

After examining each plot, a statistically significant difference could be discerned when comparing the estimated risk of progression to a haemorrhage (clinical event) between those presenting with an ICH or FND and those presenting incidentally or with a seizure in four of the cohorts (see Figure 8.11, and Figures A.1–A.2 in Appendix G), and those with a brainstem location (see Figure 8.12, and Figures A.3–A.4 in Appendix G) compared to those with another CCM location in all five studies.

The log-rank test results are given in Tables 8.9 and 8.10 below, for initial presentation and lesion location respectively in the time to first haemorrhage, and in Tables A.9–A.18 in Appendix F for the other predictors. For the other three putative predictors (age, sex and CCM multiplicity), no consistent difference was apparent (see Figures A.5–A.13 in Appendix G). In the pooled cohorts, fewer of those in the oldest age-group at diagnosis (54 years or older) appeared to have a haemorrhage or FND over five years; however, this difference was only statistically significant when the five cohorts were pooled and the log-rank test for trend was used ($\chi^2(1) = 5.05$, $p = 0.025$). Indeed, the order of the youngest group and the middle group was reversed in the three-cohort Kaplan-Meier plot for the time to clinical event analysis (see Figure A.13).

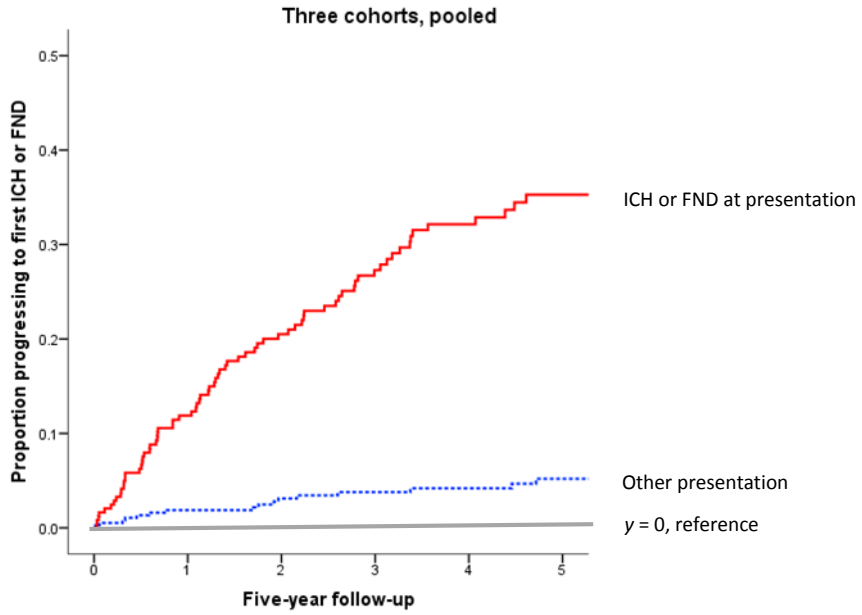
**(a)**




**Number of adults at risk (number of ICH in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **ICH or FND at presentation:** | 371 | 281(25) | 233(11) | 188(7) | 154(5) | 126(2) |
| **Other presentation:** | 617 | 539(1) | 460(6) | 397(3) | 323(2) | 271(0) |

**(b)**

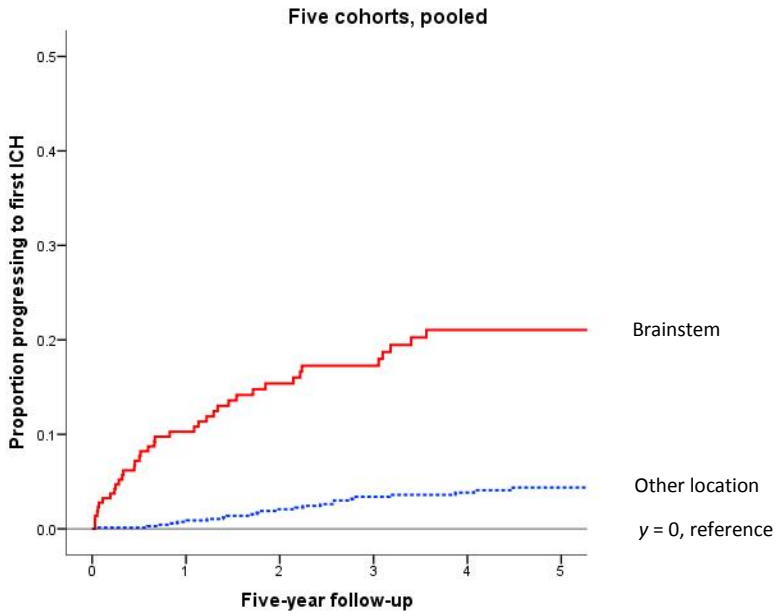



**Number of adults at risk (number of ICH in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **ICH or FND at presentation:** | 254 | 201(28) | 163(19) | 126(13) | 94(8) | 76(4) |
| **Other presentation:** | 386 | 354(7) | 307(4) | 261(2) | 208(1) | 172(2) |

**Figure 8.11 Kaplan-Meier plots comparing estimated risk of (a) first ICH and (b) first ICH or FND, stratified by presentation: ICH or FND presentation vs other presentation**

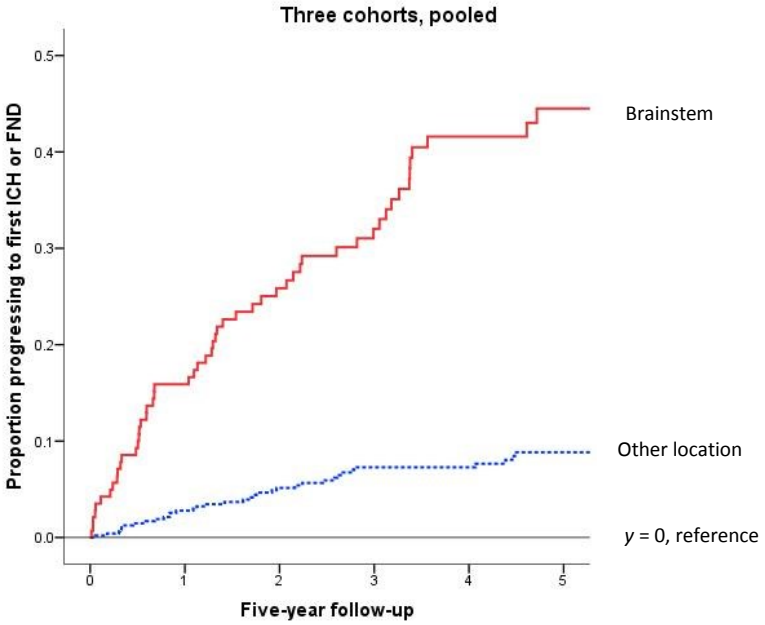
**(a)**




**Number of adults at risk (number of ICH in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Brainstem:** | 224 | 170(21) | 137(9) | 114(3) | 92(5) | 72(0) |
| **Other location:** | 764 | 650(5) | 556(8) | 471(7) | 385(2) | 325(2) |

**(b)**




**Number of adults at risk (number of ICH in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Brainstem:** | 144 | 114(22) | 90(13) | 68(7) | 47(9) | 36(2) |
| **Other location:** | 496 | 441(13) | 380(10) | 319(8) | 255(0) | 212(4) |

**Figure 8.12 Kaplan-Meier plot comparing estimated risk of (a) first ICH and (b) first ICH or FND, stratified by CCM location:brainstem vs other location**

### 8.5.2 Cox proportional hazards regression

The original intention, as outlined in Chapter 6 above and the statistical analysis plan, was to treat age in the survival analysis as a continuous variable, to avoid the loss of information, power and precision that results when a categorized variable is used (Royston, 2006). In order to do this, however, the linearity assumption had to be investigated – that is, whether the influence of age on the outcome variable can be considered to be linear. To check this assumption, age was categorized into three groups, as described in subsection 8.5.1 above. Two plots were examined: first, a Cox regression was undertaken, using age as a categorical variable, and the regression coefficients were plotted against the corresponding age-group (Machin, 2006); and second, the log minus log plots for this regression were inspected, to ascertain whether the distance between the three curves was approximately equal.

The resulting graphs seemed a little ambiguous. Furthermore, when age had been categorized into three equal-sized groups in the analysis for clinical event, the log minus log curves were not ordered. Therefore, to check that this was not an artefact, age was re-grouped into four categories (30 years or younger, 31–45 years, 46–60 years, and 61 years or older), and the analysis was repeated. This time the results were more clear-cut: the line plot resembled a Z-shape, rotated by about 40 degrees; and in the log minus log plots (Figure 8.13), the curves crossed several times, but after about 18 months, the two younger age-groups and two older age-groups separated, although the curves within these two groups crossed at least twice. Given these conflicting results, it was decided to treat age as a categorical variable with three levels, as in the subsection above: that is, 35 years or younger; 36–53 years; 54 years or older.

The unadjusted and adjusted hazard ratios for the two core pre-specified predictors for time to first ICH are presented in Tables 8.9 and 8.10; Tables A.9–A.18 (in Appendix F) display the hazard ratios for the three pre-specified putative predictors and the five pre-specified predictors (two core and three putative) for time to first clinical event.

**Table 8.9 Analysis of time to first ICH within five years of diagnosis, stratified by clinical presentation (ICH or FND at presentation vs other presentation, i.e. seizure or incidental)**

| Study | Values | Number | Events (*n*) | Log rank | *p* | Hazard ratio[a] | 95% CI | *p* | Adjusted hazard ratio[b] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mayo Clinic** | ICH or FND | 93 | 15 | 16.97 | <0.0001 | 6.37 | 2.3–7.5 | <0.0001 | 5.07 | 1.6–15.8 | 0.005 |
| | Other | 174 | 5 | | | | | | | | |
| **Toronto** | ICH or FND | 175 | 23 | 22.67 | <0.0001 | 25.64 | 3.5–189.9 | 0.001 | 17.00 | 2.2–131.1 | 0.007 |
| | Other | 170 | 1 | | | | | | | | |
| **Paris** | ICH or FND | 24 | 1 | 0.05 | 0.826 | 0.78 | 0.1–7.5 | 0.826 | 0.30 | 0.03–3.1 | 0.317 |
| | Other | 57 | 3 | | | | | | | | |
| **Scotland, 1999–2003** | ICH or FND | 38 | 5 | 7.96 | 0.005 | 7.46 | 1.4–38.5 | 0.016 | 5.51 | 0.9–32.4 | 0.059 |
| | Other | 97 | 2 | | | | | | | | |
| **Scotland, 2006–2010** | ICH or FND | 41 | 6 | 15.90 | <0.0001 | 20.58 | 2.5–171.1 | 0.005 | 7.97 | 0.9–72.4 | 0.065 |
| | Other | 119 | 1 | | | | | | | | |
| **Pooled cohorts, unstratified** | ICH or FND | 371 | 50 | 58.84 | <0.0001 | 7.96 | 4.2–15.0 | <0.0001 | 4.85 | 2.4–9.7 | <0.0001 |
| | Other | 617 | 12 | | | | | | | | |
| **Pooled cohorts, stratified by study** | ICH or FND | 371 | 50 | 55.89 | <0.0001 | 8.03 | 4.2–15.2 | <0.0001 | 4.95 | 2.5–9.9 | <0.0001 |
| | Other | 617 | 12 | | | | | | | | |

[a]Hazard ratio from univariate analysis. [b] Hazard ratio is adjusted for CCM location.

**Table 8.10 Analysis for time to first ICH within five years of diagnosis, stratified by CCM location (brainstem vs other location)**

| Study | Values | Number | Events (*n*) | Log rank | *p* | Hazard ratio[a] | 95% CI | *p* | Adjusted hazard ratio[b] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mayo Clinic** | brainstem | 63 | 10 | 9.94 | 0.002 | 3.72 | 1.5–8.9 | 0.003 | 1.59 | 0.6–4.3 | 0.356 |
| | other | 204 | 10 | | | | | | | | |
| **Toronto** | brainstem | 102 | 16 | 19.98 | <0.0001 | 5.58 | 2.4–13.0 | <0.0001 | 2.65 | 1.1–6.3 | 0.027 |
| | other | 243 | 8 | | | | | | | | |
| **Paris** | brainstem | 17 | 3 | 6.07 | 0.014 | 10.04 | 1.04–96.8 | 0.046 | 14.59 | 1.4–150.1 | 0.024 |
| | other | 64 | 1 | | | | | | | | |
| **Scotland, 1999–2003** | brainstem | 17 | 3 | 5.58 | 0.018 | 5.06 | 1.1–22.6 | 0.034 | 2.40 | 0.5–12.1 | 0.289 |
| | other | 118 | 4 | | | | | | | | |
| **Scotland, 2006–2010** | brainstem | 25 | 6 | 32.62 | <0.0001 | 40.98 | 4.9–342.2 | 0.001 | 20.92 | 2.3–190.1 | 0.007 |
| | other | 135 | 1 | | | | | | | | |
| **Pooled cohorts, unstratified** | brainstem | 224 | 38 | 63.08 | <0.0001 | 6.13 | 3.7–10.2 | <0.0001 | 3.06 | 1.8–5.4 | <0.0001 |
| | other | 764 | 24 | | | | | | | | |
| **Pooled cohorts, stratified by study** | brainstem | 224 | 38 | 59.13 | <0.0001 | 6.05 | 3.6–10.2 | <0.0001 | 3.08 | 1.8–5.4 | <0.0001 |
| | other | 764 | 24 | | | | | | | | |

[a]Hazard ratio from univariate analysis. [b] Hazard ratio is adjusted for presentation.

The results for the univariate analyses are summarized in Table 8.11 and 8.12. In the univariate analyses for each outcome event, the hazard ratios for CCM location were statistically significant for every cohort, although the hazard ratio for progression to haemorrhage ranged from 3.7 (Mayo Clinic) to 41.0 (second Scottish cohort); when the cohorts were pooled, and stratified by 'study', the hazard ratio was 6.1 (95% CI 3.6 to 10.2, $p < 0.0001$) (Table 8.10 and 8.11). For mode of clinical presentation, the unadjusted hazard ratios for four of the cohorts were statistically significant and ranged from 6.4 (Mayo Clinic) to 25.6 (Toronto); the pooled hazard ratio, stratified by 'study', was 8.0 (95% CI 4.2 to 15.2, $p < 0.0001$) (Table 8.9 and 8.11). Similarly, the hazard ratios for the two core predictors in the analysis for progression to first clinical event were statistically significant (see Table 8.12, and Tables A.13–A.14 in Appendix F). By contrast, none of the hazard ratios for the three putative predictors were statistically significant for either outcome event.

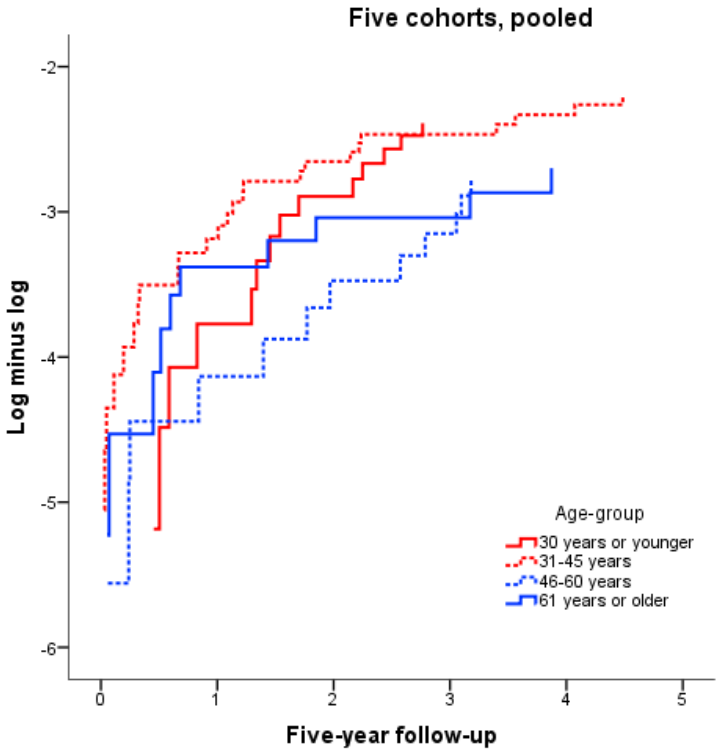



**Figure 8.13 Complementary log plot for time to first intracranial haemorrhage, stratified by four levels of age-group, to test for linearity**

**Table 8.11 Summary of the univariate analyses for the risk of haemorrhage within five years of CCM diagnosis**

| Predictor | Univariate unstratified analysis | | Univariate analysis, stratified by 'study' | | Random-effects meta-analysis | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | Hazard ratio | 95% CI | Hazard ratio | 95% CI |
| **Presentation (ICH/FND vs other)** | 7.96 | 4.2–15.0 | 8.03 | 4.2–15.2 | 7.39 | 2.9–19.2 |
| **Location (brainstem vs other)** | 6.13 | 3.7–10.2 | 6.05 | 3.6–10.2 | 5.72 | 3.2–10.3 |
| **Age: ≤ 35 years vs ≥ 54 years** | 2.10 | 1.1–4.1 | 2.11 | 1.1–4.1 | | |
| **36–53 years vs ≥ 54 years** | 1.56 | 0.8–3.1 | 1.58 | 0.8–3.1 | | |
| **Sex (female vs male)** | 0.81 | 0.5–1.3 | 0.80 | 0.5–1.3 | 0.8 | 0.5–1.4 |
| **CCM multiplicity (multiple vs solitary)** | 1.53 | 0.9–2.6 | 1.52 | 0.9–2.6 | 1.43 | 0.5–4.4 |

**Table 8.12 Summary of the univariate analyses for the risk of clinical event within five years of CCM diagnosis**

| Predictor | Univariate unstratified analysis | | Univariate analysis, stratified by 'study' | | Random-effects meta-analysis | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | Hazard ratio | 95% CI | Hazard ratio | 95% CI |
| **Presentation (ICH/FND vs other)** | 8.24 | 4.8–14.2 | 8.24 | 4.7–14.3 | 7.95 | 4.3–14.6 |
| **Location (brainstem vs other)** | 6.26 | 4.1–9.6 | 6.23 | 4.0–9.7 | 7.00 | 3.3–15.0 |
| **Age: ≤ 35 years vs ≥ 54 years** | 1.58 | 0.9–2.9 | 1.47 | 0.8–2.7 | | |
| **36–53 years vs ≥ 54 years** | 1.94 | 1.1–3.4 | 1.83 | 1.0–3.2 | | |
| **Sex (female vs male)** | 1.16 | 0.8–1.8 | 1.13 | 0.7–1.7 | 1.20 | 0.6–2.4 |
| **CCM multiplicity (multiple vs solitary)** | 0.98 | 0.6–1.6 | 0.93 | 0.6–1.6 | 0.96 | 0.6–1.6 |

## 8.6 Multivariable analysis

In the multivariable analysis, the hazard ratios of the two core predictors were adjusted for each other, and the three putative predictors were each adjusted for the two core predictors. These results are summarized in Table 8.13; more detailed results are presented in the extreme right columns of Tables 8.9 and 8.10 (for the two core predictors in the progression to first ICH analysis), and in Tables A.9–A.18 in Appendix F (the three putative predictors for the time to ICH analysis, and the two core and three putative predictors for the time to clinical event analysis).

The pooled adjusted hazard ratios for the two core predictors, clinical presentation and CCM location, each stratified by 'study', were 4.95 (95% CI 2.5 to 9.9) and 3.08 (95% CI 1.8 to 5.4) respectively for the risk of haemorrhage, and 5.20 (95% CI 2.9 to 9.4) and 3.32 (95% CI 2.1 to 5.3) respectively for the risk of clinical event.

As with the univariate analysis, the pooled hazard ratios for the two core predictors were statistically significant for both risk of haemorrhage and risk of clinical event; the adjusted hazard ratios for the three putative predictors, however, did not achieve statistical significance. This demonstrates that none of the three putative predictors – age, sex and CCM multiplicity – added statistically significant prognostic information over and above the two core predictors.

## 8.7 Meta-analysis

Two-stage random-effects meta-analyses were carried out for each of the five pre-specified predictors, and for each primary outcome; the forest plots for the two core predictors for both outcomes are displayed in Figures 8.14–8.18. In the case of the three putative predictors, two-stage random-effects meta-analyses were undertaken both for each unadjusted predictor and also for the predictor after adjusting for presentation and location (see Figures A.14–A.19 in Appendix G).

**Table 8.13 Summary of results for the multivariable analyses for both outcome events**

| Analysis | Predictor | Category | Adjusted hazard ratio* | |
|---|---|---|---|---|
| | | | Estimate | 95% CI |
| ***ICH only*** | ***Core predictors – adjusted for each other*** | | | |
| | Presentation | ICH/FND presentation | 4.95 | 2.5–9.9 |
| | Location | Brainstem | 3.08 | 1.8–5.4 |
| | ***Putative predictors – adjusted for two core predictors*** | | | |
| | Sex | Female | 0.69 | 0.4–1.1 |
| | Multiplicity | Multiple | 1.42 | 0.8–2.5 |
| | Age | ≤ 35 years | 2.34 | 1.2–4.6 |
| | | 36–53 years | 1.61 | 0.8–3.2 |
| ***ICH/FND*** | ***Core predictors – adjusted for each other*** | | | |
| | Presentation | ICH/FND presentation | 5.20 | 2.9–9.4 |
| | Location | Brainstem | 3.32 | 2.1–5.3 |
| | ***Putative predictors – adjusted for two core predictors*** | | | |
| | Sex | Female | 0.88 | 0.6–1.4 |
| | Multiplicity | Multiple | 0.82 | 0.5–1.4 |
| | Age | ≤ 35 years | 1.86 | 1.0–3.4 |
| | | 36–53 years | 2.41 | 1.4–4.3 |

**Note**
*Adjusted hazard ratios are for the pooled cohorts, stratified by 'study'.

When the five cohorts were pooled, the unadjusted hazard ratio for the effect of mode of clinical presentation on occurrence of first haemorrhage was 7.4 (95% confidence interval 2.9 to 19.2); the test for heterogeneity was not significant ($\chi^2 = 6.26$, with 4 degrees of freedom, $p = 0.18$); the estimate of between-study variance, $\tau^2$, was 0.42, and the $I^2$ index was 36% (Figure 8.14), which indicates that some heterogeneity exists. However, the Parisian cohort was very small ($n = 81$) with only four haemorrhages occurring within five years of diagnosis; it acts as a clinical outlier, as

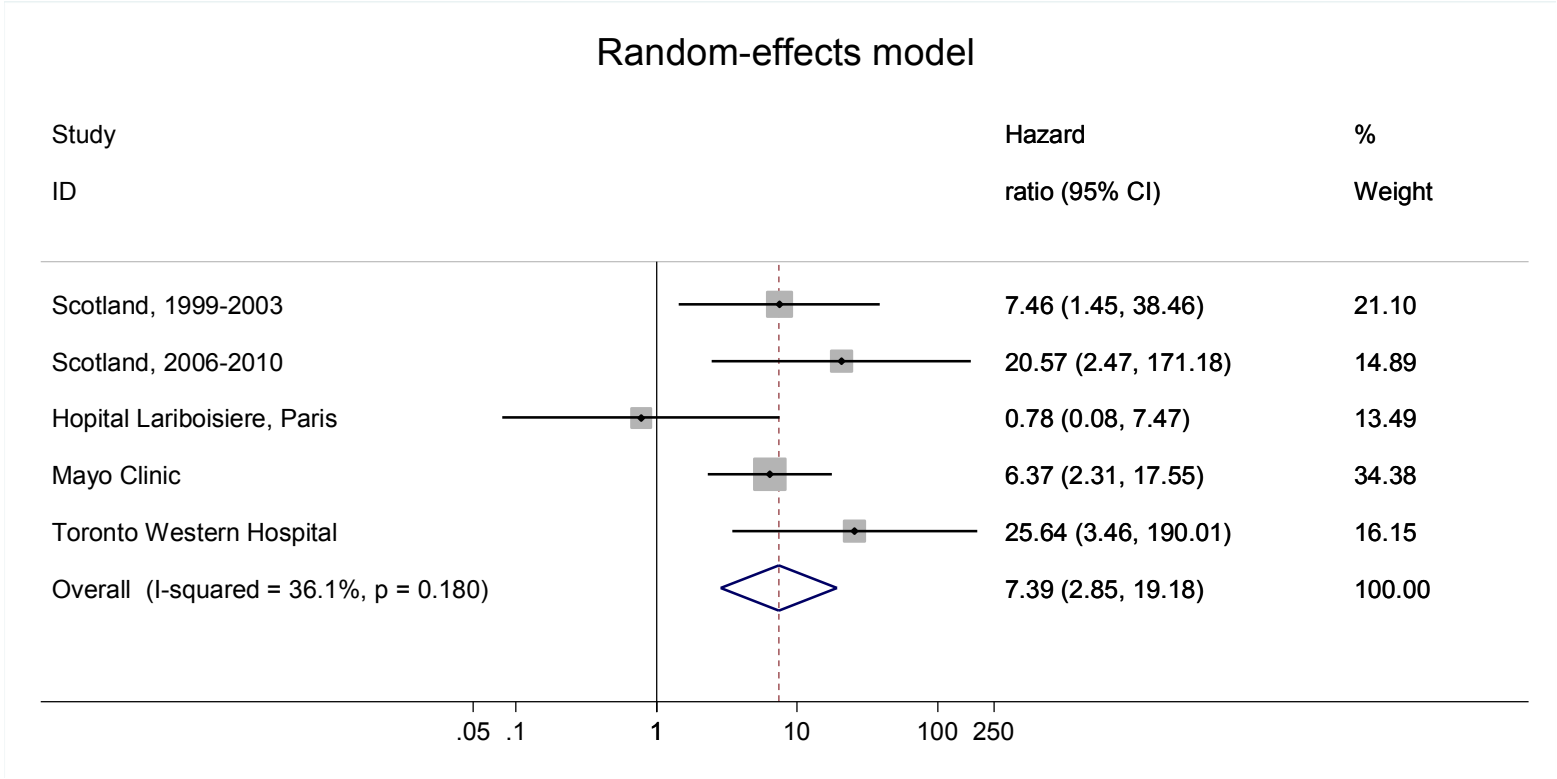
disproportionately more adults have the familial form of the disease, since the hospital is a national referral centre. When this cohort was excluded, the overall hazard ratio for the other four studies was 9.2 (95% CI 4.4 to 19.3): again, the test for heterogeneity was not significant ($\chi^2(3) = 2.13$, $p = 0.55$), but now $\tau^2 = 0$ and $I^2 = 0\%$, indicating that no heterogeneity was observed (see Figure 8.15).

Similarly, in the forest plot for the effect of CCM location on the occurrence of first ICH in five-year follow-up (Figure 8.16), the pooled (unadjusted) hazard ratio was 5.7 (95% CI 3.2 to 10.3). The test for heterogeneity was not significant ($\chi^2(4) = 4.49$, $p = 0.344$) and $\tau^2 = 0.052$. The $I^2$ value of 10.8% suggests that little variability exists between the studies that cannot be ascribed to chance.

The results are similar in the three-cohort meta-analyses of the two core predictors (see Figures 8.17 and 8.18). The unadjusted hazard ratio for mode of presentation was 7.95 (95% CI 4.3 to 14.6); the test for heterogeneity was not significant ($\chi^2(2) = 2.19$, $p = 0.344$), $\tau^2 = 0.026$, and $I^2 = 8.9\%$. The unadjusted hazard ratio for CCM location was 7.00 (95% CI 3.3 to 15.0); the test for heterogeneity was not significant ($\chi^2(2) = 4.60$, $p = 0.10$), and $\tau^2 = 0.255$; however, the $I^2$ value of 56.5% would suggest that there is high heterogeneity among these cohorts. The high value of $I^2$ can be attributed to the fact that there were only three cohorts in this meta-analysis. In the meta-analyses of the three putative predictors for haemorrhage (clinical event), none of the hazard ratios achieved statistical significance (see Figures A.14–A.19 in Appendix G).

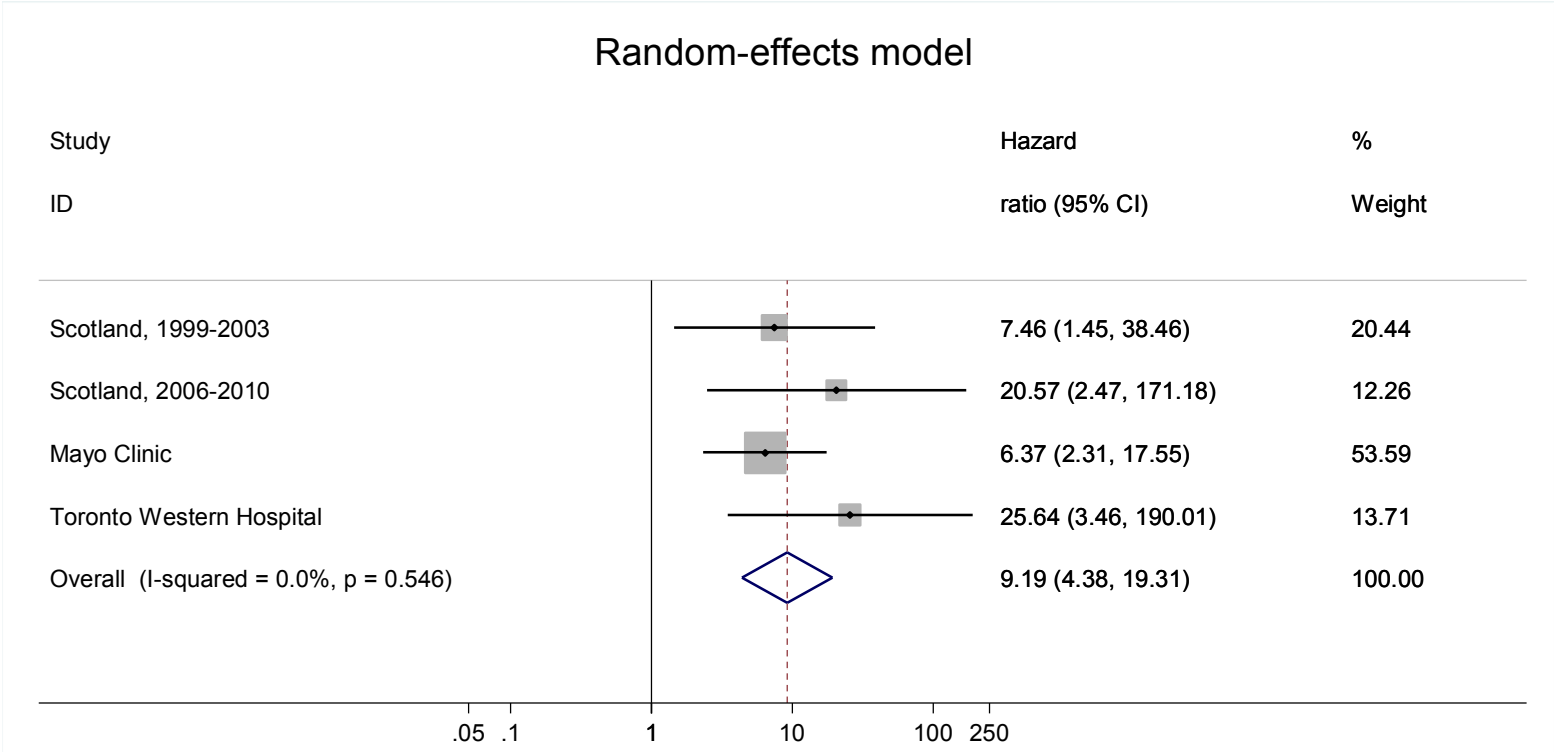
### 8.7.1 Sensitivity analyses

In the sensitivity analyses for the effect of mode of presentation and CCM location on the occurrence of intracranial haemorrhage, the equivalent unadjusted hazard ratios for the pooled cohort, stratified by 'study', were 8.03 (95% CI 4.2 to 15.2, $p < 0.0001$) and 6.05 (95% CI 3.6 to 10.2, $p < 0.0001$) respectively (see Tables 8.9 and 8.10 above for detailed results, and Tables 8.11 and 8.12 above for summarized results).



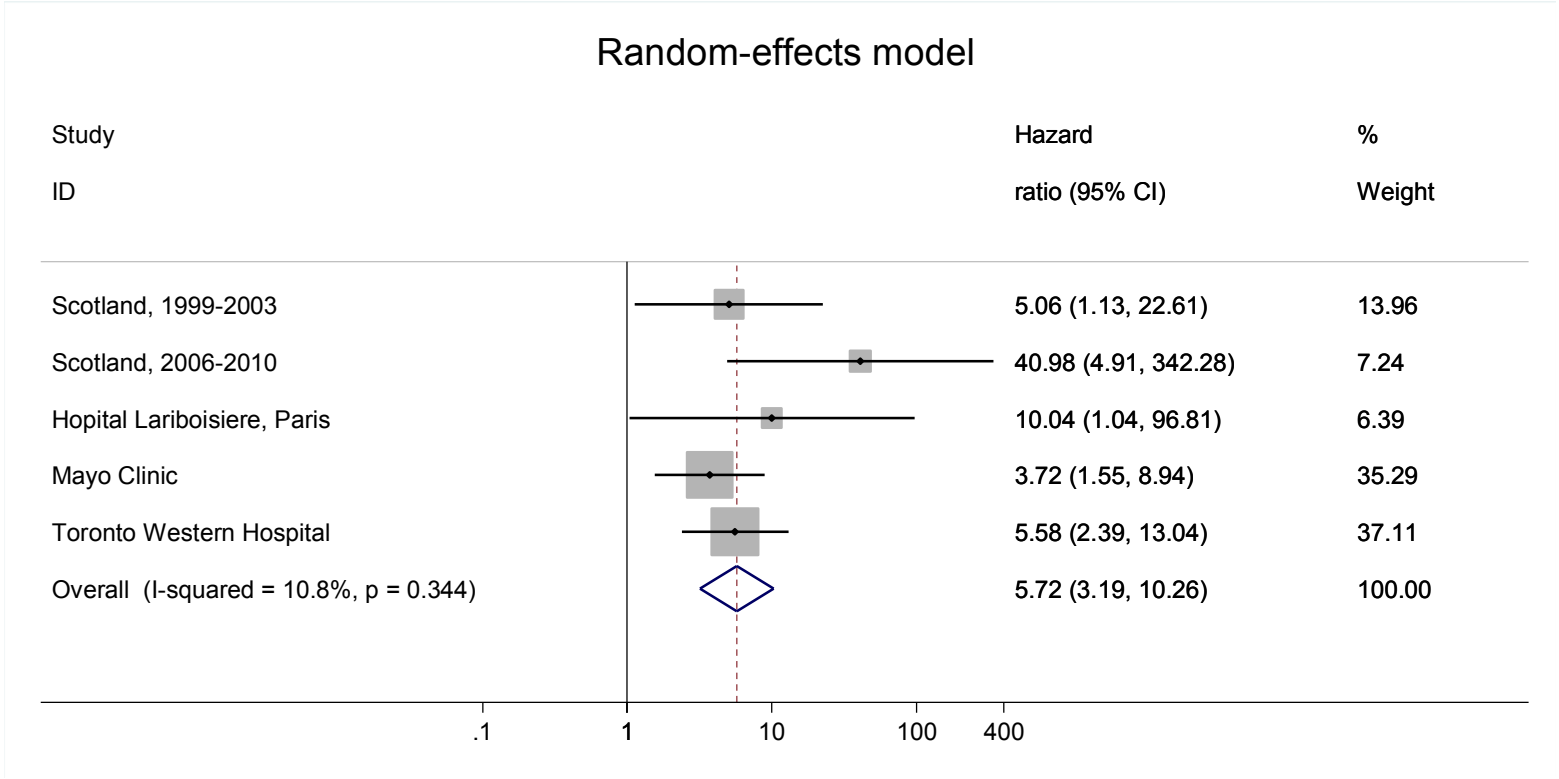

Heterogeneity
$\chi^2(4) = 6.26$, $p = 0.18$
Estimate of between-study variance, $\tau^2 = 0.4212$
Variation in effect size attributable to heterogeneity, $I^2 = 36.1\%$
Test of effect size = 1, $z = 4.11$, $p < 0.0001$

**Figure 8.14 Forest plot displaying a random-effects meta-analysis of the effect of mode of presentation (unadjusted) on the occurrence of first ICH in five-year follow-up**



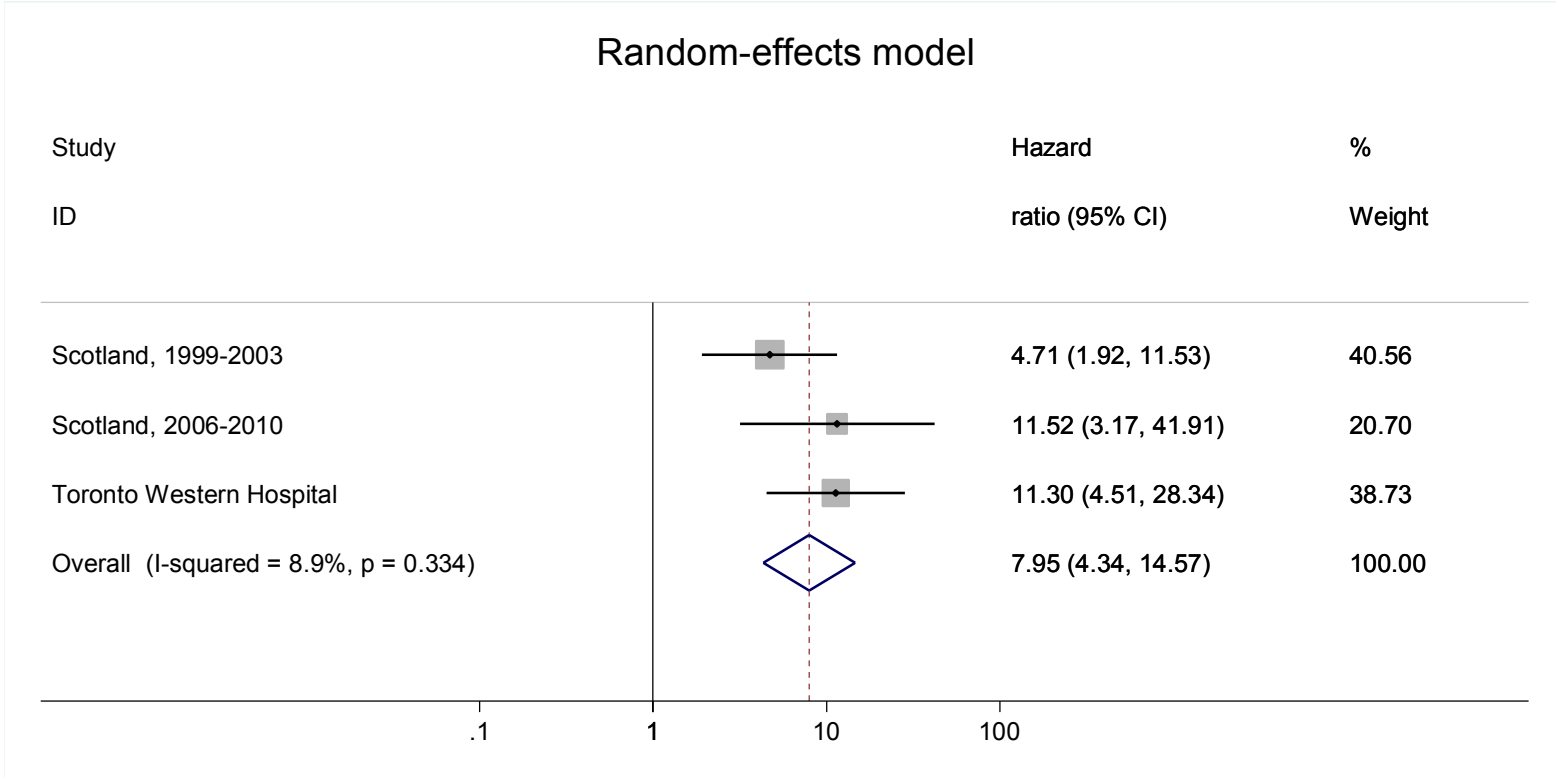

Heterogeneity
$\chi^2(3) = 2.13$, $p = 0.55$
Estimate of between-study variance, $\tau^2 = 0$
Variation in effect size attributable to heterogeneity, $I^2 = 0\%$
Test of effect size = 1, $z = 5.86$, $p < 0.0001$

**Figure 8.15 Forest plot displaying a random-effects meta-analysis of the effect of presentation (unadjusted) on occurrence of first ICH in five-year follow-up, when the smallest cohort is excluded**




Heterogeneity
$\chi^2(4) = 4.49$, $p = 0.344$
Estimate of between-study variance, $\tau^2 = 0.0515$
Variation in effect size attributable to heterogeneity, $I^2 = 10.8\%$
Test of effect size = 1, $z = 5.86$, $p < 0.0001$

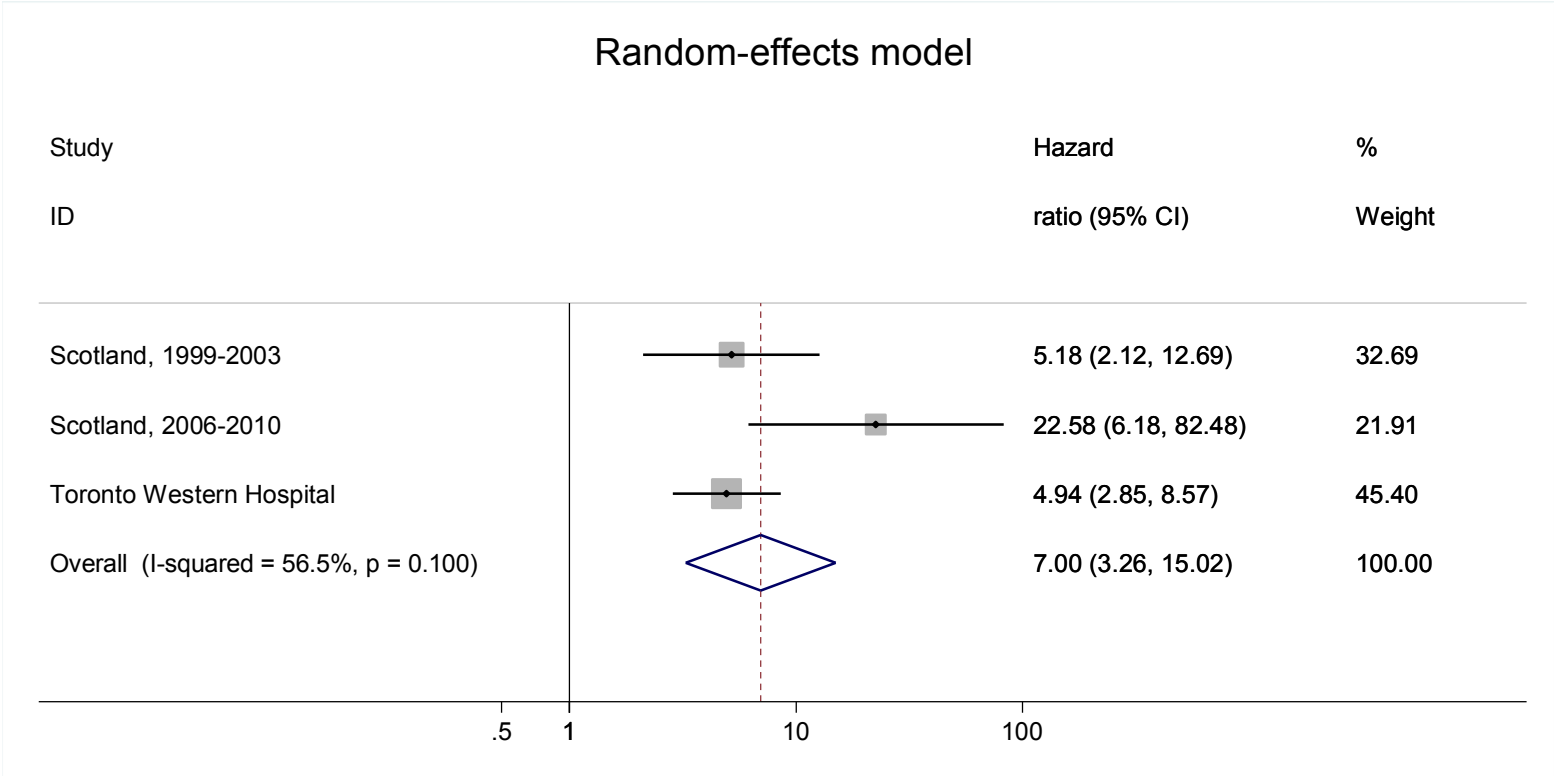
**Figure 8.16 Forest plot displaying a random-effects meta-analysis of the effect of CCM location (unadjusted) on occurrence of first ICH in five-year follow-up**




**Heterogeneity**

$\chi^2(2) = 2.19$, $p = 0.344$
Estimate of between-study variance, $\tau^2 = 0.0262$
Variation in effect size attributable to heterogeneity, $I^2 = 8.9\%$
Test of effect size = 1, $z = 6.72$, $p < 0.0001$

**Figure 8.17 Forest plot displaying a random-effects meta-analysis of the effect of mode of presentation (unadjusted) on the occurrence of first ICH or FND in five-year follow-up**




**Heterogeneity**

$\chi^2(2) = 4.60$, $p = 0.100$
Estimate of between-study variance, $\tau^2 = 0.2549$
Variation in effect size attributable to heterogeneity, $I^2 = 56.5\%$
Test of effect size = 1, $z = 5.00$, $p < 0.0001$

**Figure 8.18 Forest plot displaying a random-effects meta-analysis of the effect of CCM location (unadjusted) on occurrence of first ICH or FND in five-year follow-up**

Indeed, the confidence interval for the hazard ratio in each forest plot was slightly wider than that in the equivalent sensitivity analysis, although the level of agreement was generally good (see Tables A.9–A.15 in Appendix F).

### 8.7.2 Heterogeneity between cohorts

In Table 8.14, the baseline characteristics of the hospital-based cohorts are compared with those of the population-based cohorts to assess whether any heterogeneity exists in the study design. With regard to age, sex and CCM multiplicity, both groups are very similar. In the hospital-based cohorts, a larger proportion present with ICH or FND (42%, compared with 27% in the population-based cohorts), whereas a greater percentage of adults in the population-based cohorts present with seizure (29% compared with 22% in the hospital-based cohorts) and incidentally (44% and 35% respectively). Thus the hospital-based cohorts include a greater percentage of people with one or more potential risk factors.

In the ICH-only meta-analyses, the test of heterogeneity was only significant for the effect of multiplicity (unadjusted and adjusted): $\chi^2(3) = 7.95$, $p = 0.047$ and $\chi^2(3) = 8.90$, $p = 0.031$ respectively. (The Parisian cohort was not included in these two meta-analyses because only adults with multiple lesions suffered a haemorrhage, and therefore a hazard ratio could not be obtained for that cohort.) However, the $I^2$ index ranged from 0% (sex, adjusted for presentation and CCM location; and age unadjusted), indicating that no heterogeneity was observed, to over 60% (multiplicity, unadjusted and adjusted), which suggests that most of the variability across studies was due to heterogeneity rather than chance. Two meta-analyses – unadjusted presentation and age, adjusted for presentation and location – had respective $I^2$ values of 36% and 28%, indicating that in these meta-analyses mild heterogeneity existed between cohorts. $I^2$ values for all meta-analyses are displayed in Table 8.15.

In the meta-analyses for clinical event, only three cohorts recorded this outcome, and the test of heterogeneity was not significant for any of the predictors. An $I^2$ value of 0% was recorded for sex (adjusted for the two core predictors), unadjusted CCM multiplicity, and age (both unadjusted and adjusted). $I^2$ was equal to 9% for unadjusted

**Table 8.14 Comparison of baseline characteristics of pooled cohorts: hospital-based cohorts versus population-based cohorts**

| Characteristic | Hospital-based cohorts (*n* = 693, 70%) | | Population-based cohorts *n* = 295, 30%) | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| **Age (median, IQR)** | 44 | 32–58 | 44 | 33–57 |
| **Sex** | | | | |
| **Male** | 309 | 45% | 138 | 47% |
| **Female** | 384 | 55% | 157 | 53% |
| **Presentation** | | | | |
| **Incidental** | 246 | 35% | 129 | 44% |
| **Seizure** | 155 | 22% | 87 | 29% |
| **ICH** | 190 | 27% | 48 | 16% |
| **FND** | 102 | 15% | 31 | 11% |
| **Primary CCM location**[a] | | | | |
| **Lobar** | – | – | 210 | 71% |
| **Cerebellum** | – | – | 13 | 4% |
| **Deep** | – | – | 30 | 10% |
| **Brainstem** | 182 | 26% | 42 | 14% |
| **CCM multiplicity** | | | | |
| **Single** | 538 | 78% | 242 | 82% |
| **Multiple** | 155 | 22% | 53 | 18% |

[a] CCM location only categorized as brainstem versus other location for one cohort.

presentation, which indicates that little variability exists between cohorts that cannot be explained by chance. However, a moderate level of inconsistency existed between cohorts for unadjusted sex ($I^2$ = 45%), adjusted CCM multiplicity ($I^2$ = 51%) and unadjusted location ($I^2$ = 57%) (see Table 8.15).

**Table 8.15 $I^2$ values for all meta-analyses**

| Putative predictor | None $I^2 = 0\%$ | Very little $1\% \leq I^2 < 10\%$ | Mild $10\% \leq I^2 < 25\%$ | Moderate $25\% \leq I^2 < 50\%$ | High $I^2 > 50\%$ |
|---|---|---|---|---|---|
| **ICH only** | | | | | |
| Presentation, unadjusted | 0%[a] | | | 36.1%[b] | |
| Location, unadjusted | | | 10.8% | | |
| Sex, unadjusted | | | 11% | | |
| Sex, adjusted | 0% | | | | |
| Multiplicity, unadjusted | | | | | 62.3% |
| Multiplicity, adjusted | | | | | 66.3% |
| Age, unadjusted | 0% | | | | |
| Age, adjusted | | | | 28.2% | |
| **ICH or FND** | | | | | |
| Presentation, unadjusted | | 8.9% | | | |
| Location, unadjusted | | | | | 56.5% |
| Sex, unadjusted | | | | 44.9% | |
| Sex, adjusted | 0% | | | | |
| Multiplicity, unadjusted | 0% | | | | |
| Multiplicity, adjusted | | | | | 50.8% |
| Age, unadjusted | 0% | | | | |
| Age, adjusted | 0% | | | | |

[a] Four cohorts, exc. Paris

[b] Five cohorts.

## 8.8 Prognostic model

After completing the multivariable analysis and meta-analyses, a prognostic model was built for the estimated five-year risk of an intracranial haemorrhage (clinical event) at time of diagnosis (see the statistical analysis plan in Appendix E below). Due to the comparatively small number of outcome events, and the fact that a two-stage meta-analysis was being undertaken, the decision was taken to rely on clinical insight and prior knowledge, derived from the literature, to inform the model-building process, rather than to use stepwise selection. This decision was made to avoid the model being data-driven and over-fitted.

The default prognostic model was based on including the two core predictors that were known to affect the progression to a clinical outcome event. Previously, it was envisaged that the hazard ratios of one or more of the putative predictors would also be significant, and therefore at least one putative predictor would be a candidate for inclusion in the default model. For this reason, each of the three putative predictors was added, in turn, to the default model (i.e. the Cox regression was performed three times, with a different putative predictor being added into the analysis on each occasion), to ascertain whether any of them added further prognostic information. However, even after adjusting for the two core predictors, none of the three putative predictors achieved statistical significance. Consequently, because only the hazard ratios of the two core predictors were significant, the model-building process that was actually undertaken was much simpler than that described in both the statistical analysis plan and Chapter 6 above. Furthermore, because only two binary covariates were included in the model, the previously planned prognostic index was not created.

Therefore, as a result of the multivariable analysis, described above in section 8.6, each model contained the two core predictors: ICH or FND presentation (versus other presentation) and brainstem location (versus other location) (see Tables 8.16 and 8.17). For each outcome, over 55% of the cohort was in the low-risk, baseline group (other

presentation and other location) and about 18% in the high-risk – ICH or FND presentation, brainstem CCM – group.

For both models, the analysis was undertaken twice: first, without taking the fact that the data was pooled from five different cohorts (unstratified analysis), and second, including 'study' as a stratification. However, the results were very similar (see Tables A.19–A.20 in Appendix F below). In the following two subsections, the unstratified results are used.

### 8.8.1 Model A: four-level model

In the first model, two binary covariates – mode of clinical presentation and CCM location – were entered into a multivariable Cox regression. There are four levels for this model:

(i) incidental or seizure presentation ('other' presentation), primary CCM not located in the brainstem (i.e. 'other' location): this is the baseline or reference group;
(ii) incidental or seizure presentation, primary CCM located in the brainstem;
(iii) ICH or FND presentation, other location;
(iv) ICH or FND presentation, brainstem location.

For both outcomes (ICH or clinical event), individuals in groups (ii) to (iv), who have one or two risk factors, have a worse prognosis than those in the reference group.

For example, the hazard that an adult with a brainstem lesion who presents incidentally or with a seizure might suffer a haemorrhage within five years of diagnosis is more than three times that for an adult with a similar presentation, but whose lesion is in a non-brainstem location (HR = 3.1; 95% CI 1.8 to 5.4). For an adult presenting with an ICH or FND and a non-brainstem lesion, the comparable hazard is almost five times the baseline hazard (HR = 4.9; 95% CI 2.4 to 9.7). However, the hazard ratio for an adult with both risk factors – brainstem CCM, ICH or FND presentation – is almost 15 relative to an adult in the baseline category (HR = 14.9; 95% CI 4.3 to 51.8) (see Table 8.16).

**Table 8.16 Four-level prognostic model: hazard ratios and estimated five-year risk of outcome event**

| Predictor | Adults | | ICH (ICH/FND) in 5-year follow-up | Hazard ratio | 95% confidence intervals | Estimate of 5-year risk | 95% confidence intervals |
|---|---|---|---|---|---|---|---|
| | *n* | % | | | | | |
| **ICH only** | | | | | | | |
| ICH/FND presentation, brainstem location | 173 | 18% | 36 | 14.9 | 4.3 to 51.8 | 25.7% | 18.3 to 33.2 |
| ICH/FND presentation, other location | 198 | 20% | 14 | 4.9 | 2.4 to 9.7 | 10.6% | 5.2 to 16.1 |
| Other presentation, brainstem location | 51 | 5% | 2 | 3.1 | 1.8 to 5.4 | 5.5% | 0 to 12.9 |
| Other presentation, other location | 566 | 57% | 10 | 1.0 | - | 2.4% | 0.9 to 3.8 |
| **ICH or FND** | | | | | | | |
| ICH/FND presentation, brainstem location | 113 | 18% | 48 | 16.3 | 5.7 to 46.3 | 50.7% | 40.1 to 61.4 |
| ICH/FND presentation, other location | 141 | 22% | 24 | 5.1 | 2.8 to 9.1 | 22.4% | 14.2 to 30.6 |
| Other presentation, brainstem location | 31 | 5% | 5 | 3.2 | 2.0 to 5.1 | 22.9% | 3.7 to 42.2 |
| Other presentation, other location | 355 | 56% | 11 | 1.0 | - | 3.7% | 1.5 to 5.9 |

**Table 8.17 Three-level prognostic model: hazard ratios and estimated five-year risk of outcome event**

| Risk factor | Adults | | ICH (ICH/FND) in 5-year follow-up | Hazard ratio | 95% confidence intervals | Estimate of five-year risk | 95% confidence intervals |
|---|---|---|---|---|---|---|---|
| | *n* | % | | | | | |
| **ICH only** | | | | | | | |
| Two risk factors | 173 | 18% | 36 | 14.3 | 7.1 to 28.8 | 25.7% | 18.3 to 33.2 |
| One risk factor | 249 | 25% | 16 | 4.0 | 1.8 to 8.7 | 9.5% | 4.9 to 14.1 |
| No risk factors | 566 | 57% | 10 | 1.0 | | 2.4% | 0.9 to 3.8 |
| **ICH or FND** | | | | | | | |
| Two risk factors | 113 | 18% | 48 | 18.0 | 9.4 to 34.8 | 50.7% | 40.1 to 61.4 |
| One risk factor | 172 | 27% | 29 | 6.1 | 3.1 to 12.2 | 22.3% | 14.8 to 29.8 |
| No risk factors | 355 | 56% | 11 | 1.0 | | 3.7% | 1.5 to 5.9 |

The prognosis is similar when comparing the risk of an ICH or FND within five years of diagnosis: the hazard for those who have both risk factors is more than 16 times that for those in the reference group (HR = 16.3; 95% CI 5.7 to 46.3) (see Table 8.16).

*Model A: linear predictors*

Expression 8.1 below represents the linear predictor for the estimated five-year risk of an intracranial haemorrhage at time of diagnosis, in untreated follow-up, and expression 8.2 represents the equivalent linear predictor for the five-year risk of a clinical event in untreated follow-up (see also Table 8.18 below). In expression 8.1, 1.12 is the log hazard ratio for CCM location, and 1.58 is the log hazard ratio for mode of presentation; similarly, in expression 8.2, the coefficients are the respective log hazard ratios for each predictor.

$$\mathbf{1.12}x_1 + \mathbf{1.58}x_2 \qquad \mathbf{8.1}$$

$$\mathbf{1.162}x_1 + \mathbf{1.627}x_2 \qquad \mathbf{8.2}$$

where $x_1$ = 0, if the CCM is not located in the brainstem (i.e. 'other location'), and
$x_1$ = 1, if the CCM is located in the brainstem; and
$x_2$ = 0, if mode of presentation is seizure or incidental, and
$x_2$ = 1, if ICH or FND presentation.

## 8.8.2 Model B: three-level model

In the second model, the two groups with a single risk factor have been combined, as their hazard ratios are similar; thus the three levels of this model are no, one and two risk factors (see Table 8.17). The rationale for developing this model is twofold: first, a three-level model will provide more stable estimates in the category with the fewest members (other presentation, brainstem location); and second, the three-level model might be more practical for clinical use, as it is slightly simpler. (See section 9.1.1 below for a discussion concerning the two models.)

**Table 8.18 Model A: analysis and linear predictor equation**

| Outcome | Prognostic factor | Category | Estimated coefficient (*b*) | Standard error (*b*) | Wald test | Hazard ratio | | Linear predictor |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Estimate | 95% CI | |
| **ICH only** | Presentation | ICH or FND | 1.580 | 0.351 | 20.22 | 4.85 | 2.438–9.665 | |
| | | Other | | | | 1.00 | | |
| | Location | Brainstem | 1.120 | 0.285 | 15.44 | 3.06 | 1.753–5.357 | |
| | | Other | | | | | | |
| | | | | | | | | 1.58 * presentation + 1.12 * location |
| **ICH or FND** | Presentation | ICH or FND | 1.627 | 0.299 | 29.69 | 5.09 | 2.834–9.134 | |
| | | Other | | | | 1.00 | | |
| | Location | Brainstem | 1.162 | 0.235 | 24.34 | 3.20 | 2.014–5.070 | |
| | | Other | | | | 1.00 | | |
| | | | | | | | | 1.63 * presentation + 1.16 * location |

**Table 8.19 Model B: analysis and linear predictor equation**

| Outcome | Prognostic factor | Category | Estimated coefficient (*b*) | Standard error (*b*) | Wald test | Hazard ratio | | Linear predictor |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Estimate | 95% CI | |
| **ICH only** | Risk factor | Two | 2.66 | 0.36 | 55.28 | 14.28 | 7.09–28.79 | |
| | | One | 1.38 | 0.40 | 11.63 | 3.96 | 1.80–8.72 | |
| | | None | | | | 1.00 | | |
| | | | | | | | | 1.38 * risk factor |
| **ICH or FND** | Risk factor | Two | 2.89 | 0.34 | 74.64 | 18.05 | 9.36–34.7 | |
| | | One | 1.81 | 0.35 | 26.10 | 6.11 | 3.05–12.22 | |
| | | None | | | | 1.00 | | |
| | | | | | | | | 1.81 * risk factor |

As in Model A, for both outcomes, the group with no risk factors is the baseline. The hazard ratio that an individual with a single risk factor might suffer an intracranial haemorrhage within five years of diagnosis is 4.0 (95% CI 1.8 to 8.7) relative to those in the reference group, and for an adult with two risk factors, the hazard ratio is more than 14 compared to the reference group (HR = 14.3, 95% CI 7.1 to 28.8). Similarly, the hazard for a person with a single risk factor suffering either a haemorrhage or focal neurological deficit within five years of diagnosis is over six times that for someone with no risk factors (HR = 6.1, 95% CI 3.1 to 12.2), and for an individual with both risk factors this hazard increases to 18 (95% CI 9.4 to 34.8).

*Model B: linear predictors*

Expression 8.3 represents the linear predictor for the estimated five-year risk of a first intracranial haemorrhage at time of diagnosis, in untreated follow-up, and expression 8.4 represents the equivalent linear predictor for the estimated five-year risk of a clinical event in untreated follow-up (see also Table 8.19).

$$\mathbf{1.375}x_1 + \mathbf{2.659}x_2 \qquad \mathbf{8.3}$$

$$\mathbf{1.809}x_1 + \mathbf{2.893}x_2 \qquad \mathbf{8.4}$$

where $x_1 = 0$ and $x_2 = 0$, represents no risk factors,

$x_1 = 1$ and $x_2 = 0$, represents one risk factor, and

$x_1 = 0$ and $x_2 = 1$, represents two risk factors.

However, in this model, there is a single predictor with three levels, so the two linear predictors for Model B can be simplified, as shown in Table 8.19, by writing them as

1.38 × (number of risk factors) ICH

and

1.81 × (number of risk factors) clinical event.

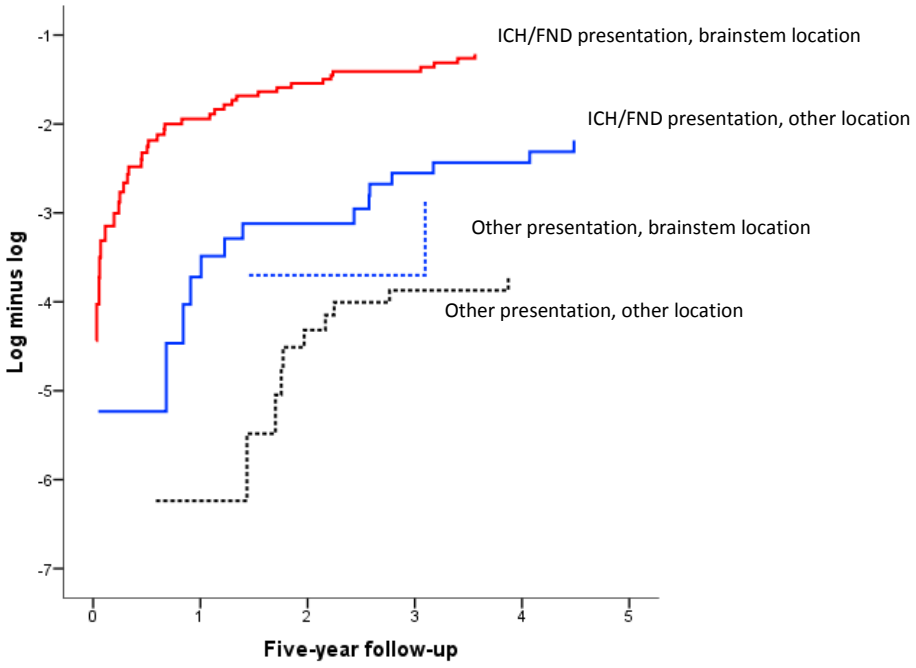
### 8.8.3 Proportional hazards assumptions

Log-minus-log plots were inspected to check that the proportional hazards assumptions for both models are valid (Figure 8.19). In the plots for time to first intracranial haemorrhage and first clinical event in five-year follow-up in model A (Figure 8.19a and c), three of the four curves were parallel; however, there were insufficient outcome events in the brainstem location/other presentation group to enable a meaningful curve to be plotted. (In Figure 8.19c the brainstem location/other presentation curve cut two of the parallel curves, but this is almost certainly an artefact due to paucity of outcome events.) Therefore it is not possible to obtain very robust estimates in the four-way split, because one category had very few outcome events. In contrast, the three curves were parallel for both outcomes in Model B (Figure 8.19b and d).

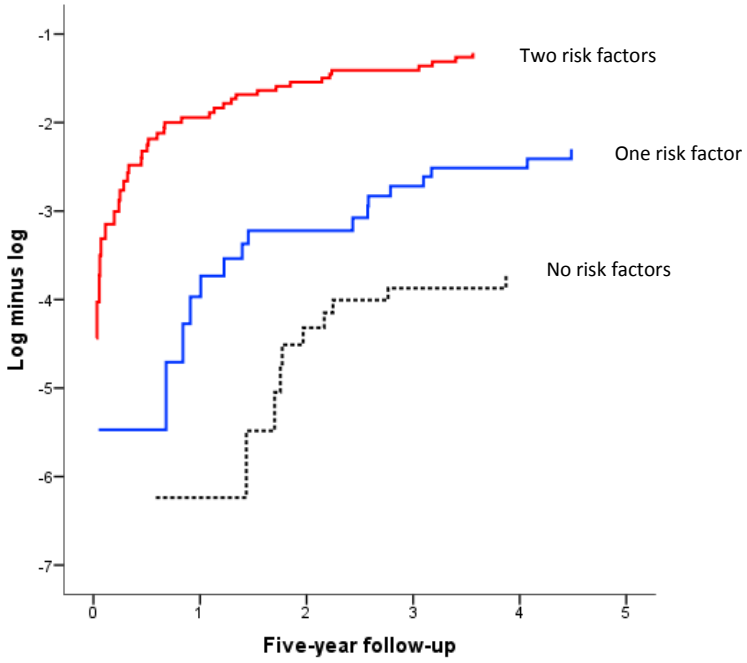
### 8.8.4 Discrimination

Originally, I had assumed that the model would include at least one putative predictor, in addition to the two core predictors; if this had been the case, then a prognostic index would have been created, as described in Chapter 6 above (subsection 6.6.8). However, as the model contained only two binary predictors, the study population was automatically divided into four groups (or three, if the two groups with a single risk factor were combined), without creating a prognostic index. In order to assess the level of separation between predictors, Kaplan-Meier plots were produced for each outcome in each model, as described below.

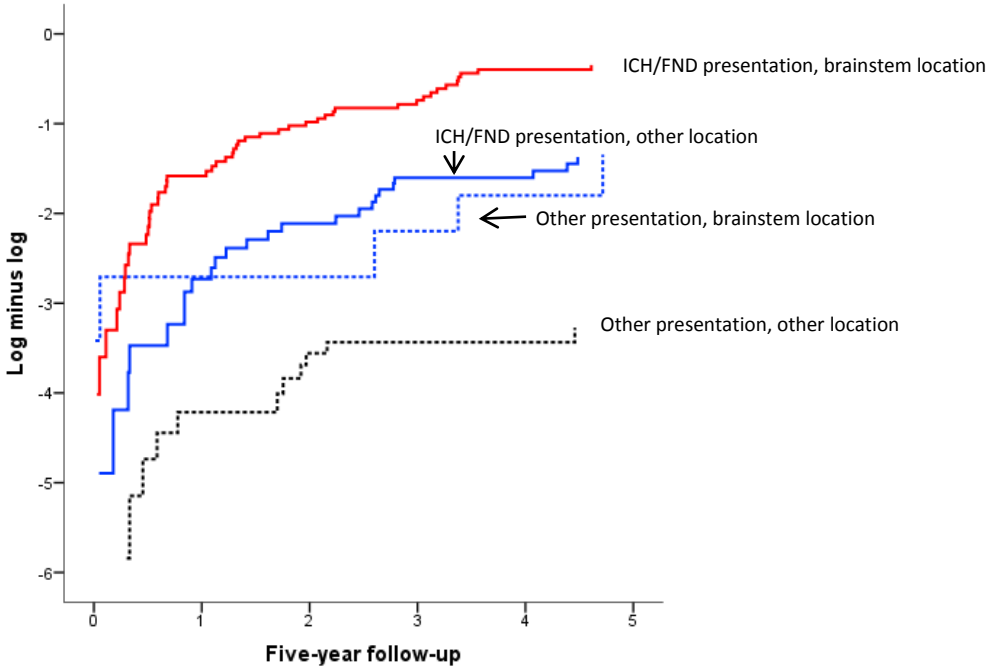
**(a) ICH: by mode of clinical presentation and CCM location (Model A)**




**(b) ICH: by risk factor (Model B)**



**(c) Clinical event: by mode of clinical presentation and CCM location (Model A)**




**(d) Clinical event: by risk factor (Model B)**

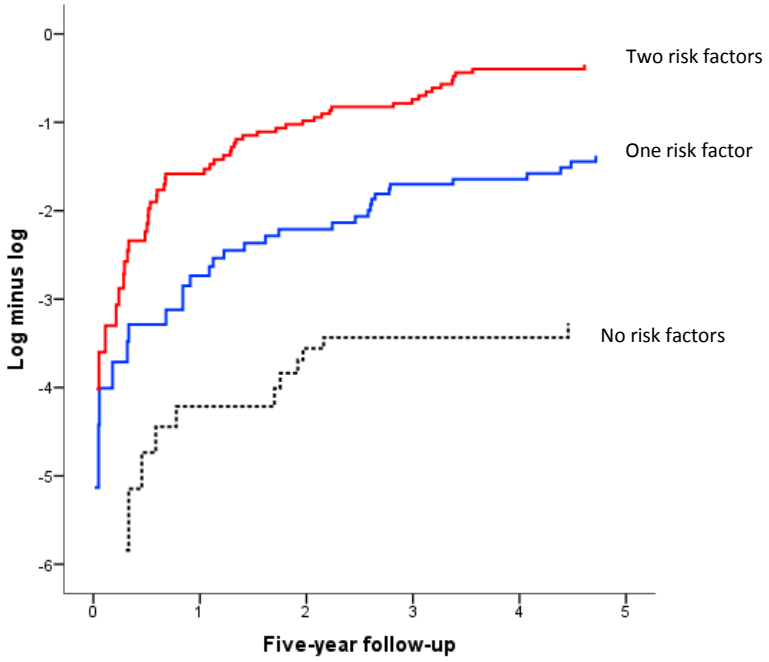



**Figure 8.19 Test of the proportional hazards assumption, using log minus log plots, for intracranial haemorrhage (a) by presentation and location and (b) risk factor, and for clinical event (ICH or FND) by presentation and location and (d) risk factor**

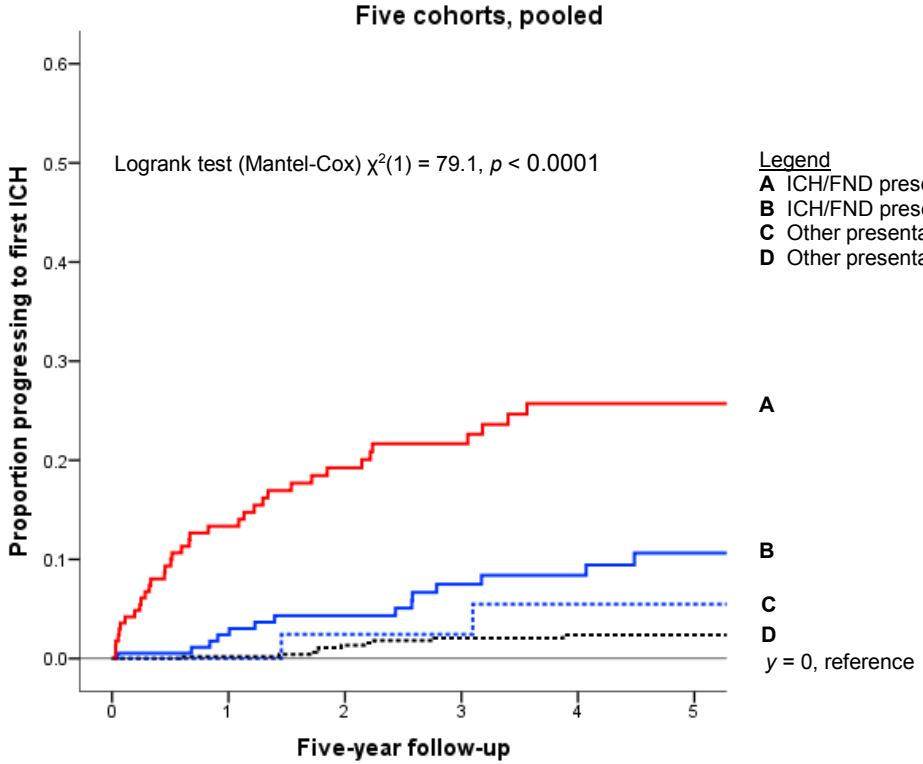
### Model A

For this model, a Kaplan-Meier plot was produced for each outcome (ICH or clinical event), stratified by the four levels: (i) other presentation and other CCM location (baseline reference group), (ii) other presentation and brainstem location, (iii) ICH/FND presentation and other location, and (iv) ICH/FND presentation and brainstem location (see Figures 8.20 and 8.21). As can be observed, for each outcome there are clear differences in the risk of progression to an ICH (clinical event) among the four groups, and those with the two risk factors have a statistically significant higher risk than those with a single or no risk factor (ICH only, log-rank test: $\chi^2(1) = 79$, $p < 0.0001$; ICH or FND, log-rank test: $\chi^2(1) = 114$, $p < 0.0001$).

There is a wide gap between those with the worst prognosis (a brainstem CCM and ICH or FND presentation) and the next-worse prognosis group (ICH or FND presentation with a lesion in a different location) for both outcomes, but in the Kaplan-Meier plot for composite outcome, the survival curves for those who present with an ICH/FND, with a lesion in another location, and those with a brainstem CCM and incidental or seizure presentation are quite close and cross over twice. This latter fact adds weight to the proposition to create a model with three levels – no risk factors, one or two risk factors – as developed in model B.

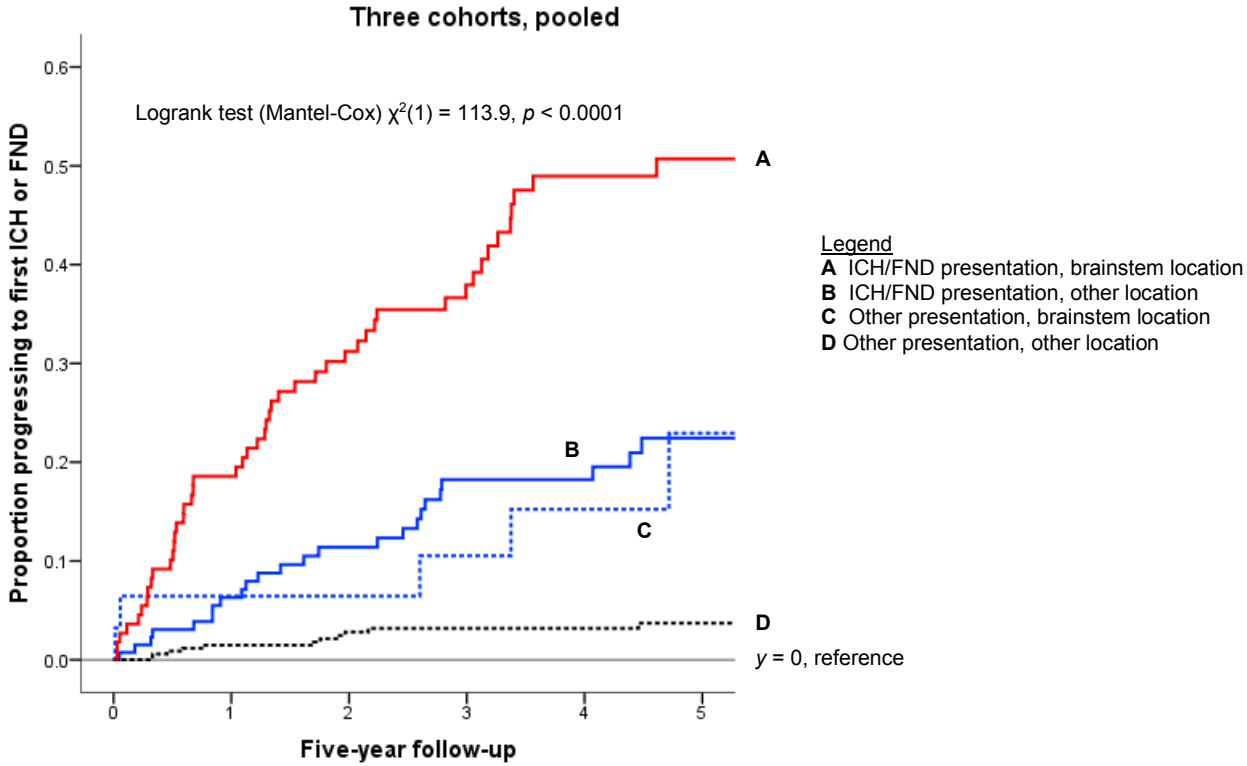
For each risk group, the Kaplan-Meier estimated risk of a first ICH (clinical event) within five years of diagnosis, together with 95% confidence intervals, is presented in Figure 8.22. The estimates for each outcome for the baseline group, represented in black, are ranged to the left of the figure, with values between 0% and 6%; estimates for the group who have both risk factors (shown in red) are situated to the right of the figure, reflecting the increased risk of a haemorrhage (clinical event).

The Kaplan-Meier estimated risk of haemorrhage within five years of diagnosis for those in the Paris cohort who have a brainstem lesion and present incidentally or with a seizure is greater than for those in the same cohort who have both risk factors, but the confidence intervals for the former estimate are so large that that point estimate is



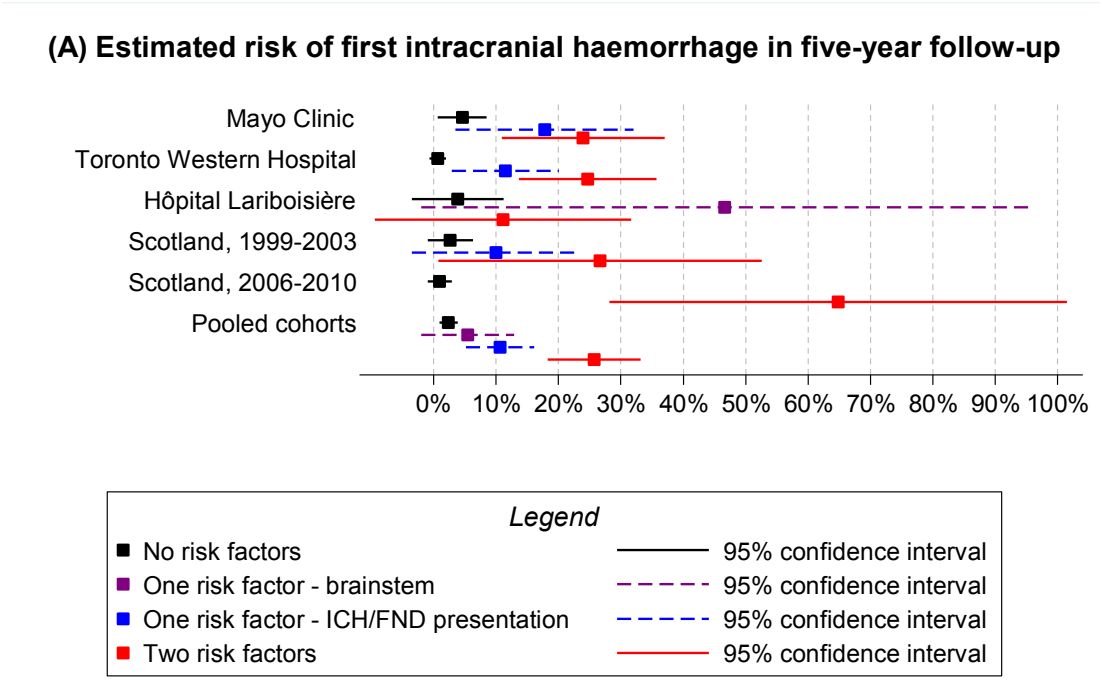

| Number of adults at risk (number of ICH in preceding year): | | | | | | |
|---|---|---|---|---|---|---|
| **ICH/FND, brainstem** | 173 | 125(21) | 101(8) | 82(3) | 65(4) | 57(0) |
| **ICH/FND, other location** | 198 | 156(4) | 132(3) | 106(4) | 89(1) | 69(2) |
| **Other presentation, brainstem** | 51 | 45(0) | 36(1) | 32(0) | 27(1) | 15(0) |
| **Other presentation, other location** | 566 | 494(1) | 424(5) | 365(3) | 296(1) | 256(0) |

**Figure 8.20 Kaplan-Meier plot of estimated risk of ICH within five years of diagnosis, stratified by mode of presentation and CCM location**




| Number of adults at risk (number of ICH in preceding year): | | | | | | |
|---|---|---|---|---|---|---|
| **ICH/FND, brainstem** | 113 | 86(20) | 66(13) | 48(6) | 31(8) | 27(1) |
| **ICH/FND, other location** | 141 | 115(8) | 97(6) | 78(7) | 63(0) | 49(3) |
| **Other presentation, brainstem** | 31 | 28(2) | 24(0) | 20(1) | 16(1) | 9(1) |
| **Other presentation, other location** | 355 | 326(5) | 283(4) | 241(1) | 192(0) | 163(1) |

**Figure 8.21 Kaplan-Meier plot of estimated risk of clinical event within five years of diagnosis, stratified by presentation and CCM location**



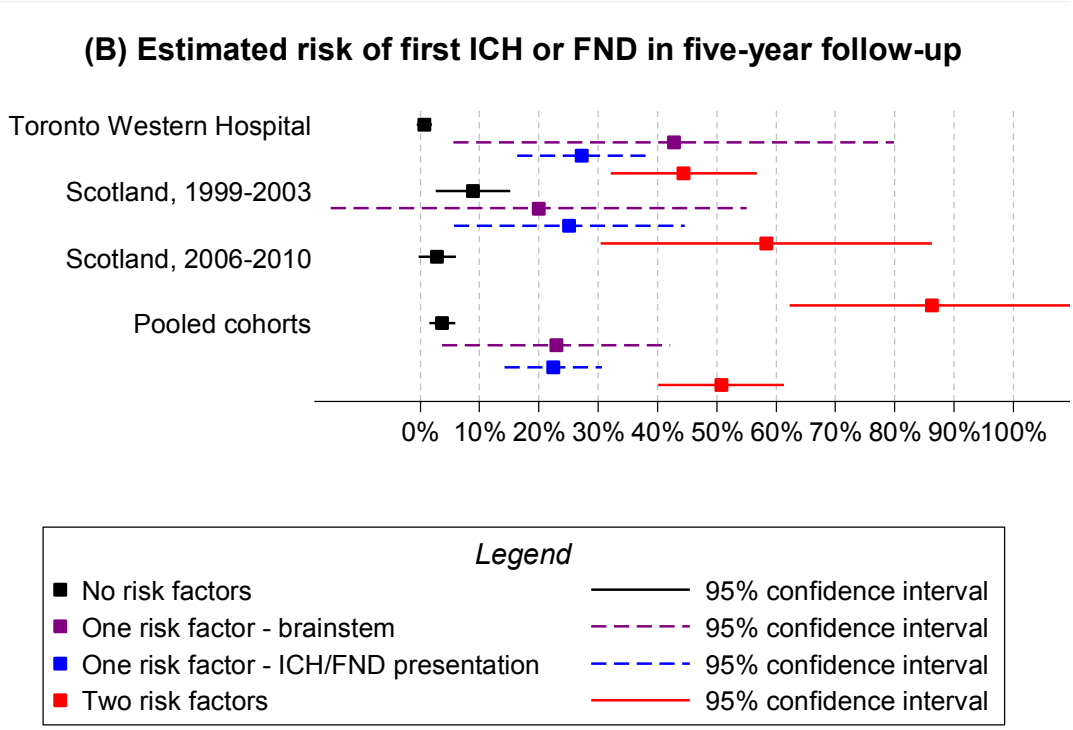



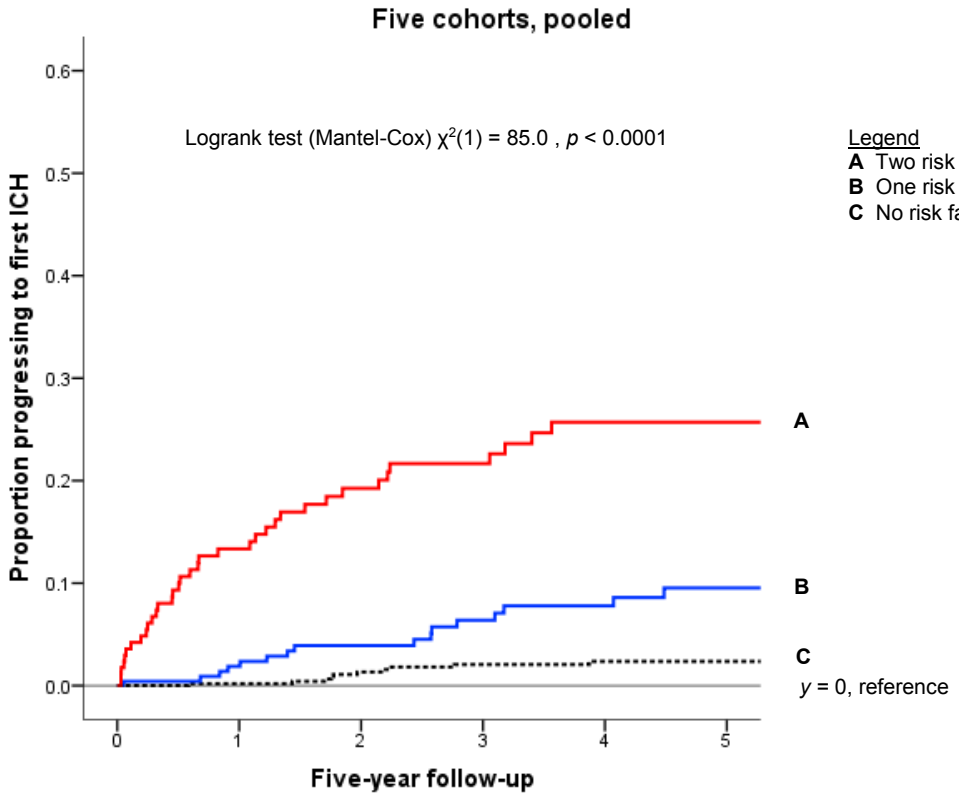

**Figure 8.22 Model A: estimated risk of first ICH or clinical event within five years of diagnosis**

rendered meaningless. However, the Paris cohort is different to the other cohorts: it is much smaller; there are comparatively fewer haemorrhages in follow-up; and a greater percentage of adults harbour multiple lesions, as the hospital specializes in the familial form of the disease.

### Model B

Again, Kaplan-Meier plots were used to investigate the degree of separation between the three groups – no risk factors, one or two risk factors – for each outcome, and the survival curves are displayed in Figures 8.23 and 8.24. Progression to first ICH (clinical event) is very different, depending on how many risk factors are present, and the log-rank test is statistically significant for both outcomes (intracranial haemorrhage: $\chi^2(1) = 85$, $p < 0.0001$; clinical event: $\chi^2(1) = 124$, $p < 0.0001$). For the composite outcome (ICH or FND, see Figure 8.24), the three curves are slightly more evenly spaced than for the single outcome (ICH, Figure 8.23), although the distance between the curves for none and one risk factor is smaller than that between one and two risk factors.

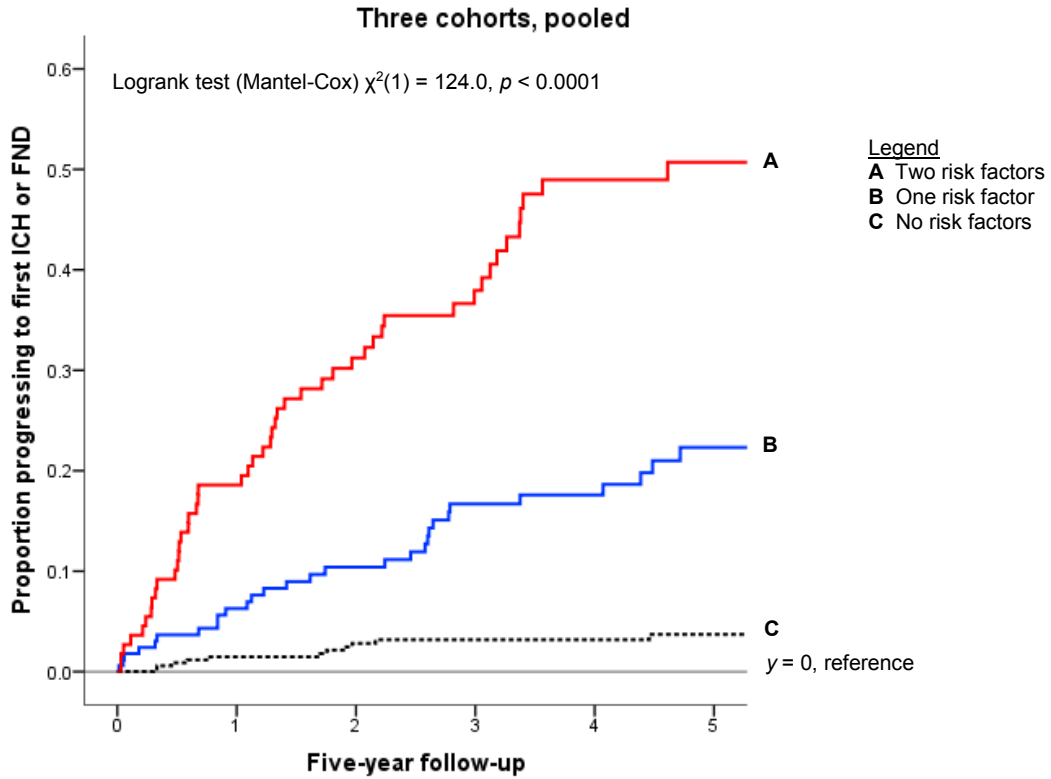
The Kaplan-Meier estimated risk of a first haemorrhage (clinical event) in five-year follow-up is presented in Figure 8.25; apart from the Paris cohort, the separation into three groups is very good, especially for the composite outcome.




**Number of adults at risk (number of ICH in preceding year):**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Two risk factors** | 173 | 125(21) | 101(8) | 82(3) | 65(4) | 57(0) |
| **One risk factor** | 249 | 201(4) | 168(4) | 138(4) | 116(2) | 84(2) |
| **No risk factors** | 566 | 494(1) | 424(5) | 365(3) | 296(1) | 256(0) |

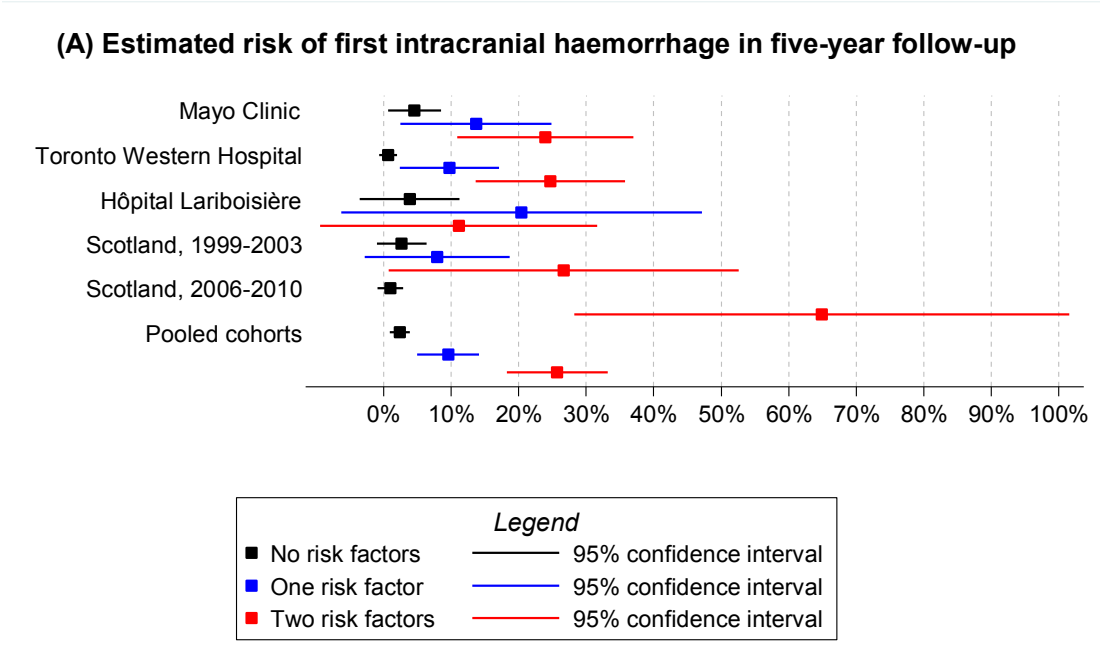
**Figure 8.23 Kaplan-Meier plot of estimated risk of ICH within five years of diagnosis, stratified by risk factors**




**Number of adults at risk (number of ICH or FND in preceding year):**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Two risk factors** | 113 | 86(20) | 66(13) | 48(6) | 31(8) | 27(1) |
| **One risk factor** | 172 | 143(10) | 121(6) | 98(8) | 79(1) | 58(4) |
| **No risk factors** | 355 | 326(5) | 283(4) | 241(1) | 192(0) | 163(1) |

**Figure 8.24 Kaplan-Meier plot of estimated risk of ICH or FND within five years of diagnosis, stratified by risk factors**



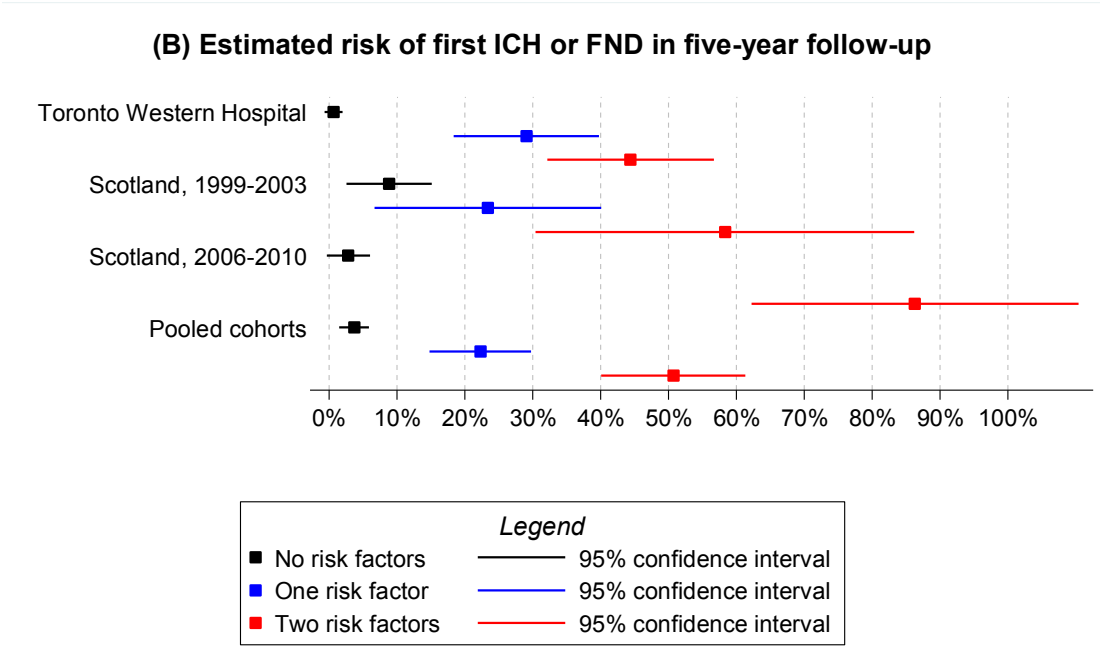




**Figure 8.25 Model B: estimated risk of first ICH or clinical event within five years of diagnosis**

## 8.9 Subsidiary analysis

In the analysis of the effect of sex on the recurrence of an intracranial haemorrhage within five years of CCM diagnosis, 262 adults from the five cohorts either presented with a haemorrhage ($n$ = 238, 91%) or suffered one within five years of diagnosis (twelve adults presented with an FND, six with a seizure and six incidentally). Of these, 44 participants (17%) – 23 women (15%) and 21 men (19%) – had a recurrent haemorrhage within five years of diagnosis.

A comparison of the baseline characteristics of those who experienced a recurrent haemorrhage within five years of diagnosis and those who suffered a single haemorrhage, either at diagnosis or within five-year follow-up, is presented in columns 2–6 of Table 8.20. All the characteristics have a similar distribution in the two groups, with the exception of CCM location: 68% of those who have a recurrent ICH have a brainstem lesion, whereas only 39% have a brainstem lesion in the group who do not experience a recurrence within five years of diagnosis.

A Kaplan-Meier plot showing time to recurrent haemorrhage, stratified by sex, is displayed in Figure 8.26(a); there was no statistically significant difference in the risk of haemorrhage between the two sexes (log-rank test $\chi^2(1) = 0.91$, $p = 0.34$).

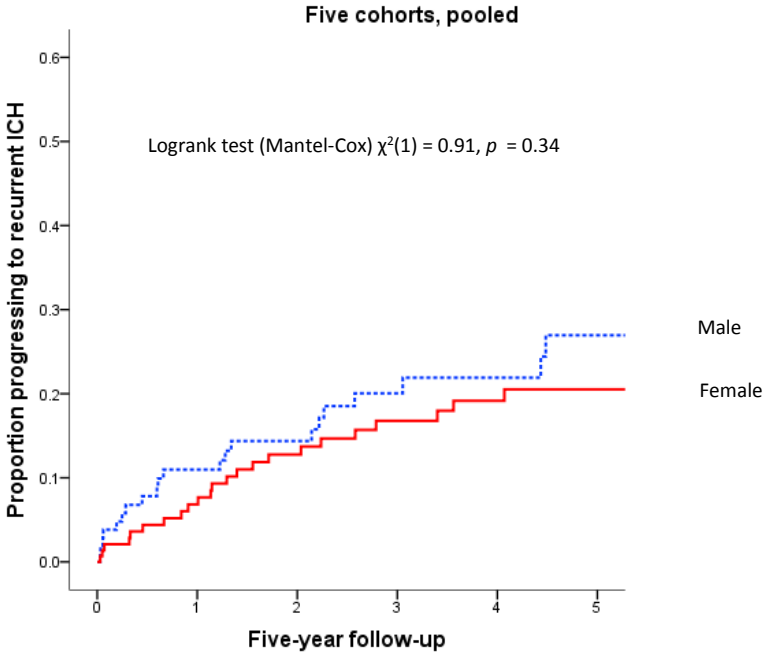
Similarly, in the three cohorts where focal neurological deficits in follow-up were recorded, 272 adults either presented with an intracranial haemorrhage or a focal neurological deficit ($n$ = 256, 94%) or experienced an event within five years of CCM diagnosis (11 presented incidentally and five with a seizure). In this analysis, 76 adults (28%) suffered a recurrent ICH or FND within five years of diagnosis: 31 men (26%) and 45 women (29%). The baseline characteristics of those who suffered a recurrent ICH or FND and those who did not are compared in columns 7–11 of Table 8.20. Again, there is a similar distribution within the two groups with the exception of CCM location: 65% of those who experience a recurrence have a brainstem lesion, compared to 36% of those who do not.

In the stratified Kaplan-Meier survival plot for time to recurrent clinical event, the estimated risk of an event in five-year follow-up did not differ significantly between men and women (log-rank test, $\chi^2(1) = 0.08$, $p = 0.77$; see Figure 8.26(b)).

**Table 8.20 Baseline characteristics of adults who have experienced an ICH (ICH or FND), stratified by recurrence**

| | Recurrent ICH, five cohorts | | | | | Recurrent ICH or FND, three cohorts | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Recurrence | | No recurrence | | Total | Recurrence | | No recurrence | | Total |
| | *n* | *%* | *n* | *%* | | *n* | *%* | *n* | *%* | |
| Age at diagnosis (median, IQR) | 42 | 33-50 | 40 | 30–53 | 40, 31–53 | 41 | 34-51 | 43 | 33–57 | 43, 34–55 |
| Sex | | | | | | | | | | |
| Male | 21 | *48%* | 89 | *41%* | 110 | 31 | *41%* | 87 | *44%* | 118 |
| Female | 23 | *52%* | 129 | *59%* | 152 | 45 | *59%* | 109 | *56%* | 154 |
| Mode of clinical presentation | | | | | | | | | | |
| Incidental | 1 | *2%* | 5 | *2%* | 6 | 4 | *5%* | 7 | *4%* | 11 |
| Seizure | 1 | *2%* | 5 | *2%* | 6 | 0 | *0%* | 5 | *3%* | 5 |
| ICH | 38 | *86%* | 200 | *92%* | 238 | 43 | *57%* | 121 | *62%* | 164 |
| FND | 4 | *9%* | 8 | *4%* | 12 | 29 | *38%* | 63 | *32%* | 92 |
| CCM location | | | | | | | | | | |
| Brainstem | 30 | *68%* | 85 | *39%* | 115 | 49 | *65%* | 70 | *36%* | 119 |
| Other location | 14 | *32%* | 133 | *61%* | 147 | 27 | *36%* | 126 | *64%* | 153 |
| CCM multiplicity | | | | | | | | | | |
| Single | 32 | *73%* | 168 | *77%* | 200 | 63 | *83%* | 146 | *75%* | 209 |
| Multiple | 12 | *27%* | 50 | *23%* | 62 | 13 | *17%* | 50 | *26%* | 63 |

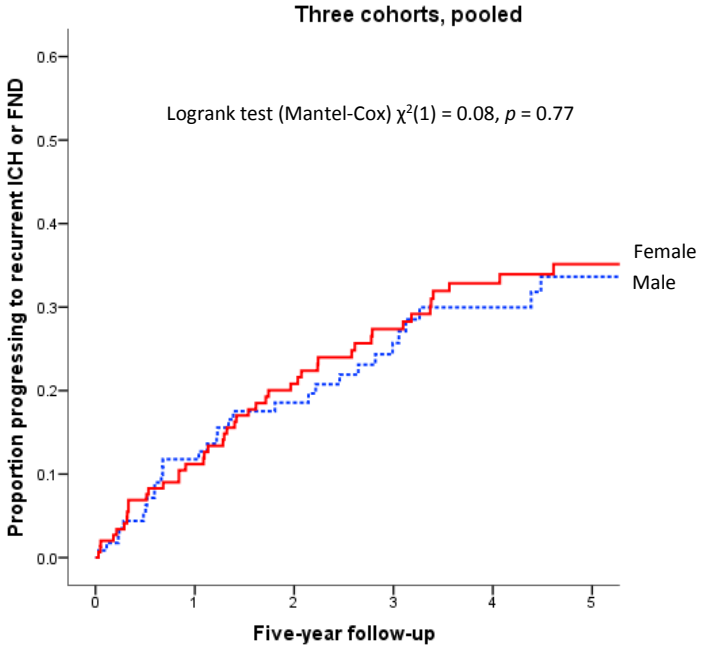
**(a)**




**Number of adults at risk (number of ICH in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Female** | 152 | 113(9) | 93(7) | 74(4) | 59(2) | 47(1) |
| **Male** | 110 | 83(11) | 63(3) | 45(4) | 33(1) | 29(2) |

**(b)**




**Number of adults at risk (number of ICH/FND in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Female** | 154 | 122(16) | 102(13) | 82(8) | 63(6) | 51(2) |
| **Male** | 118 | 95(13) | 75(7) | 55(6) | 41(3) | 33(2) |

**Figure 8.26 Kaplan-Meier plots comparing estimated risk of recurrent (a) ICH or (b) clinical event, stratified by sex**

# Chapter 9: Discussion

## 9.1 Prognostic model

### 9.1.1 Model A or B?

In this study, two risk factors have been identified that are associated with an increase in an adult's likelihood of experiencing an intracranial haemorrhage (or clinical event) within five years of diagnosis, assuming no interventional treatment has occurred: ICH or FND presentation (versus other presentation) and brainstem CCM location (versus other location). Conversely, the three putative risk factors – age, sex and CCM multiplicity – do not appear to add any statistically significant prognostic information to the model.

In the previous chapter (section 8.8), two versions of a prognostic model that was fitted to the data were described. Model A had four levels: (i) baseline, no risk factors (i.e. other presentation and other location); (ii) other presentation, brainstem location; (iii) ICH/FND presentation, other location; and (iv) ICH/FND presentation, brainstem location. In Model B, levels (ii) and (iii) were combined to form the following levels: (a) no risk factor; (b) one risk factor; and (c) two risk factors.

The motivation for creating a prognostic model is to stratify the risk of an intracranial haemorrhage (clinical event) within five years of diagnosis for adults who have not received interventional treatment for their cerebral cavernous malformation. In Figures 8.20–8.21 (Model A) and 8.23–8.24 (Model B), Kaplan-Meier plots were examined to assess the ability of each model to discriminate between the various risk groups.

Although these plots illustrate the fact that adults who possess both risk factors have a considerably greater risk of experiencing either outcome, the four-level model discriminates less well between adults in the other three groups. (Note that in Table 8.16 above, the 95% confidence intervals for the estimated five-year risk overlap in the groups who have no or one risk factor, for both outcome events.) In contrast, there is a good level of separation between the three trajectories in Model B, demonstrating a very different prognosis for each risk group (see also Table 8.17).

This difficulty in achieving robust estimates in the four-level model arises because, in the five-cohort analysis of time to ICH, there are only two (out of 62) outcome events in one category (those who present incidentally or with a seizure, but have a brainstem lesion). In Model B, an assumption has been made that adults who have a single risk factor – whether ICH/FND presentation or brainstem CCM – have the same risk of progressing to a haemorrhage or clinical event. If clinicians are able to accept this assumption – even though, from a clinical view, an adult with a brainstem CCM presenting with a seizure or incidentally is very different to an adult with a CCM in another (i.e. non-brainstem) location presenting initially with an ICH or FND – then Model B would be the better model to adopt, since it provides more robust estimates, because each category has an adequate number of outcome events with which to estimate the risk.

When the composition of the other presentation / brainstem location group was examined more closely, it was discovered that the group consists of 51 adults (5.2%), two of whom suffered a haemorrhage within five years of diagnosis. However, both these adults were in the Parisian cohort, the composition of which differs from the other four cohorts (see sections 8.7 above and 9.2.1 below). This provides further evidence that Model B should be adopted, since the estimated risk of ICH would be zero, if the Parisian cohort were to be excluded from the study, as there would be no outcome events in the other presentation / brainstem location group.

### 9.1.2 Uses of the model

As was apparent in Figures 8.23 and 8.24, Model B provides a good level of separation for the three risk groups, and results for this model were presented in Table 8.17. The estimated risk of an intracranial haemorrhage within five years of diagnosis, with no interventional treatment, can be stratified thus:

| | |
|---|---|
| no risk factors | 2.4% (95% CI 0.9 to 3.8) |
| one risk factor | 9.5% (95% CI 4.9 to 14.1) |
| two risk factors | 25.7% (95% CI 18.3 to 33.2) |

With model B, the 95% confidence intervals for the point estimate (five-year risk) for each risk group do not overlap, demonstrating a complete separation of risk groups; this is also true for the clinical event analysis (see Table 8.17).

The likelihood ratio statistic (*LR*) was used to test the predictive ability of each of Models A (the four-group model) and B (the risk-factor model) (using the $-2$ log likelihood, $LL_1$ ) against the null model (with no predictors, and the $-2$ log likelihood, $LL_0$ ), where

$$LR = -2(LL_0 - LL_1).$$

The $-2$ log likelihood, $LL_0$ value for the null model was 820.93 and the $-2$ log likelihood, $LL_1$ for models A and B was 748.50 and 749.22 respectively. Therefore the likelihood ratio statistics for Models A and B were equal to 72.43 and 71.71, each with two degrees of freedom (as there were two covariates in Model A and three levels of risk factor in Model B). However, Model B is not nested within Model A, so the likelihood ratio test cannot be used (Harrell et al., 1984, Machin et al., 2006). There is no significant difference between the fit of the two models (although both are an improvement on the null model), but Model B is preferred because it is the simpler model and demonstrates a slightly better separation of the risk groups.

A major advantage of model B is its simplicity, which is of benefit to both the clinician and the patient. For the clinician, the model can be used as an adjunct in describing the prognosis to patients at the time of diagnosis of cerebral cavernous malformation, if the lesion is conservatively managed. More importantly, for the patient, the results of the model are easy to understand and may help to give them some sense of perspective about their disease and its prognosis. Information is available at the time of diagnosis about an estimated risk of haemorrhage (or clinical event) occurring within five years of diagnosis, if the lesion is conservatively managed, given the presence or absence of the two risk factors. However, it must be borne in mind that the model relates only to the risk of a haemorrhage or focal neurological deficit in untreated follow-up; the risk of epileptic seizures, which can also be very debilitating, is not included in this model.

In addition to providing the patient with more information about the likely progression of the disease, the result of this study may influence the decision of how the disease should be managed (see subsection below). For a patient with a lesion located in the lobar area of the brain who presents incidentally (i.e. a patient in the reference group who has no risk factors), the estimated risk of a haemorrhage or focal neurological deficit within five years is sufficiently low that a decision to undergo interventional treatment would be an unlikely choice of management, given the risks that are related to brain surgery, unless the patient suffered intractable epilepsy. However, if the patient has a brainstem lesion and presented with a haemorrhage (i.e. has both risk factors), then the increased risk of a subsequent haemorrhage or focal neurological deficit within five years, compared to the baseline risk, may be sufficient to render the prospect of neurosurgery, with its various associated risks, less unappealing, especially as several researchers have emphasized the risk of permanent neurological deficit after two or more bleeds (Aiba et al., 1995, Porter et al., 1999, Kuker and Forsting, 2008, Recinos et al., 2011).

## Adults treated during follow-up

During the five-year follow-up period, 107 adults (10.8%) were censored at the time of interventional treatment, before they had experienced either outcome, as was described in section 8.3 above. In Table 9.1, these adults are examined, according to their risk group and initial mode of clinical presentation. Although over 50% of those who were treated are in the low-risk group (i.e. no risk factors), 47 adults presented with a seizure and thus were more likely to be undergoing surgical excision as a result of intractable epilepsy. Only eight adults who presented incidentally (1.4% of those who had neither risk factor) were censored for treatment. By contrast, 19 adults who possessed both risk factors (11.0% of this high-risk group) were censored for treatment.

**Table 9.1 Adults censored for treatment, stratified by risk group**

| Risk groups | Risk group | | Adults censored for treatment | | Mode of presentation | Adults |
|---|---|---|---|---|---|---|
| | $n_R$ | *%n* | $n_T$ | % $n_R$ | | $n_T$ |
| **Neither risk factor** | 566 | *57.3%* | 55 | *9.7%* | Incidental<br>Seizure | 8<br>47 |
| **One risk factor** | 249 | *25.2%* | 33 | *13.3%* | | |
| ***Brainstem location*** | *51* | *5.2%* | 1 | *2.0%* | Incidental | 1 |
| ***ICH/FND presentation*** | *198* | *20.0%* | 32 | *16.2%* | ICH<br>FND | 28<br>4 |
| **Both risk factors** | 173 | *17.5%* | 19 | *11.0%* | ICH<br>FND | 15<br>4 |

***n*** Number of adults in five-cohort study (*n* = 988).
$n_R$ Number of adults in each risk group.
$n_T$ Number of adults who were censored for treatment.

## 9.2 The study

### 9.2.1 Strengths

Three main strengths are associated with this study: the size of the cohort, the length of follow-up, and the consistency of the results across studies. To my knowledge, this is the largest collaborative study to explore the risk of intracranial haemorrhage (clinical event) in newly diagnosed adults who have not received interventional treatment for their cavernous malformation.

#### Study size

To have sufficient power for the potential inclusion of the five putative predictors in a prognostic model, sixty outcome events (haemorrhages) were required, as age is analysed as a categorical variable (Concato et al., 1995, Peduzzi et al., 1995, Harrell et al., 1996). Fortunately for the patient, however (if not the statistician), outcome events are not particularly common for adults with this condition. In the five cohorts included in this study, 62 outcome events (ICH) were observed; the percentage of adults who experienced a haemorrhage in the five-year follow-up period varied between 4.4% (the later Scottish cohort) and 7.5% (Mayo Clinic). In addition, although cerebral cavernous malformation does not qualify as a rare disease, it is not particularly common: the annual population-based first-CCM detection rates in Scotland between 1999 and 2003 (2006 and 2010) were 0.69 (0.78) per 100,000 adults. Therefore to achieve the requisite number of outcome events within a reasonable time-period, a collaborative study was required, with the inevitable differences in patient population and study protocol that would ensue.

### Consistency of results across studies

As a consequence of the potential for clinical heterogeneity among the different patient populations, random-effects meta-analyses were undertaken. This method of meta-analysis has an additional source of uncertainty compared with the fixed-effect method, and this uncertainty is reflected in the fact that the confidence intervals are wider for random-effects than fixed-effect meta-analysis. In reality, there was no statistically significant heterogeneity between the cohorts, and this was particularly the case if the Paris cohort was excluded (for example, compare Figures 8.14 and 8.15). In sensitivity analyses, the results of the meta-analyses were compared with the results obtained when the pooled cohort was stratified by 'study'; the smaller the amount of heterogeneity existing between cohorts, the closer the confidence interval in the meta-analysis was to that in the stratified cohort.

Despite the fact that all the cohorts were from observational studies rather than trials, and thus there were potential differences in the patient populations, there was a high level of consistency in the results: namely, a brainstem location was found to be a statistically significant risk factor in all five cohorts, and ICH or FND presentation was statistically significant in the four larger cohorts. The hazard ratios for the effect of lesion location on occurrence of haemorrhage ranged from 3.7 (95% CI 1.6 to 8.9) (Mayo Clinic) to 41.0 (95% CI 4.9 to 342.3) (the later Scottish cohort) (see Figure 8.16), and hazard ratios for presentation ranged from 0.8 (95% CI 0.1 to 7.5) (Paris) to 25.6 (95% CI 3.5 to 190.0) (Toronto) (Figure 8.14). As was demonstrated in section 8.7 above, however, the smaller cohort from Paris contained a larger proportion of adults with the familial form of the disease, because the French National Reference Centre for Rare Neurovascular Diseases of the Eye and Brain is located at Hôpital Lariboisière, whereas the other cohorts comprised mostly adults with the sporadic form. Thus if the Paris cohort were excluded on grounds of its small size and highly selected status, the range of hazard ratios for the effect of presentation on occurrence of haemorrhage became 6.4 (95% CI 2.3 to 17.6) (Mayo Clinic) to 25.6 (95% CI 3.5 to 190.0) (Toronto) (Figure 8.15).

Although the two core predictors were statistically significant in the majority of the individual-cohort analyses, it was only by pooling the data into a large single cohort that a more precise estimate of the effect of these two risk factors could be achieved for each outcome event in the pooled cohort. For example, the pooled estimate for the effect of location on occurrence of haemorrhage was 5.7 (95% confidence interval 3.2 to 10.3); the equivalent estimate for presentation was 7.4 (95% CI 2.9 to 19.2), and if the hazard ratio is based on the four larger cohorts, the pooled estimate is 9.2 (95% CI 4.4 to 19.3).

### Length of follow-up

Another strength of this study is the length of follow-up. Among the five pooled cohorts the median length of follow-up was 3.9 years (interquartile range 1.5–5.0 years). Although the target of five years was not achieved, 50% of the patients contributed almost four years' follow-up, during which period the majority of haemorrhages and focal neurological deficits are likely to occur.

The decision to truncate follow-up at five years was taken for several reasons. Primarily, the follow-up period for a study of this nature needs to be sufficiently long to enable outcome events to occur; however, the results of previous studies have suggested that after a certain period of time, the risk of a first intracranial haemorrhage or focal neurological deficit decreases (Al-Shahi Salman et al., 2012). In addition, five years' follow-up seemed potentially to be a length of time that most studies could achieve. Even in the second Scottish cohort, where recruitment ended on 31 December 2010 and therefore five years' follow-up for everyone in the study was not possible, the median length of follow-up was 3.9 years (interquartile range 2.9–5.0 years), which compared favourably with two of the other cohorts. A third reason motivating five-year truncation was a desire to encourage a standardized length of follow-up for future studies, to enable inter-study comparison.

### External validity

The fact that this study is a collaboration of four research groups from four different countries is important, since this will increase the external validity of the result. Two of the cohorts were population-based, representing all known instances of a first CCM diagnosis in a single country within two five-year periods. In contrast, the other three studies were hospital-based: Toronto Western Hospital is a tertiary neurosurgical referral centre, which might be expected to see a disproportionately large number of more severe cases. Research groups at Hôpital Lariboisière in Paris specialize in rare vascular diseases of the brain and are involved with much research into the genetic aspects of the disease; this is reflected in the composition of the Parisian cohort, since this cohort includes a larger percentage of adults with multiple cavernous malformations (a feature of the genetic form of the disease). The Mayo Clinic is a tertiary-care referral centre that attracts patients from all over the world, in addition to those who live in the immediate geographical vicinity of its Minnesota location. Despite these different backgrounds, the five cohorts were broadly similar at baseline (see Tables 8.1 and 8.2 above), the level of heterogeneity was small, and there was a very high level of consistency across the results.

## 9.2.2 Limitations

There are, however, limitations to this study. First, there appears to be a lack of similar cohorts, and in particular prospective population-based studies. It was difficult to identify other research groups who had collected data in a similar manner, and who were willing to collaborate. Several groups who had published their results in the 1990s, at a time when the use of MRI was becoming more widespread and consequently the detection of CCMs more frequent, were contacted and invited to join this collaboration. Unfortunately, however, as described in section 7.1 above, a number of these groups had since disbanded or the data were no longer available.

Because of the challenges relating to the recruitment of studies to collaborate in this individual patient data meta-analysis, it was not possible to split the dataset into two groups, and use one to develop the model and the other to validate it. Therefore before the model can be used in clinical practice, it should be validated on a different dataset.

Another limitation is the paucity of data concerning the occurrence of focal neurological deficit in follow-up. Only three cohorts were able to contribute data for this outcome, which is unfortunate because the effects of an FND can be as devastating to the patient and family as those of an ICH. However, this is a common consequence of using secondary data, since the data have originally been collected for specific, but frequently different purposes. Nevertheless, the situation contributed to a tension in the study embodied in the following analysis dilemma: on the one hand, there were more cohorts, but with fewer outcome events (haemorrhages) available for analysis, whereas on the other hand, fewer cohorts contributed data, but more outcome events (ICH or FND) could be included in the analysis.

### Informative censoring

As discussed in Chapter 8 above (section 8.3), 107 participants (10.8%) underwent treatment within five years of diagnosis and before a potential haemorrhage occurred, and thus are at risk of informative censoring. However, as shown in Table 9.2, at least 51 adults (47.7%) received interventional treatment as a result of intractable epilepsy, and were perhaps less at risk of experiencing a haemorrhage if they had been conservatively managed throughout the entire follow-up period.

As illustrated in Table 8.3, the 47 participants (4.8%) who presented with an ICH or FND, and in addition had less than two years of follow-up, are at greatest risk of informative censoring. However, when the baseline characteristics of those adults who were treated during follow-up, and before an event could occur ($n$ = 107), were compared with the remainder of the study ($n$ = 881) (see Table 8.4), the treated group were significantly younger (median age 37.5 years versus 45.2 years respectively, Mann Whitney test, $p < 0.0001$); in addition, they were more likely to present with an ICH or FND (48% versus 36%) or seizure (44% versus 22%) ($\chi^2(2) = 49.4$, $p < 0.0001$).

**Table 9.2 Number censored for treatment, by cohort and treatment reason**

| Cohort | Treated | Seizure-related | ICH/FND-related | Unknown |
|---|---|---|---|---|
| **Mayo Clinic** | 56 | 35 | 13 | 8 |
| **Toronto** | 16 | 2 | 7 | 7 |
| **Paris** | 4 | 2 | – | 2 |
| **Scotland, 1999–2003** | 19 | 8 | 6 | 5 |
| **Scotland, 2006–2010** | 12 | 4 | 7 | 1 |
| **Total** | 107 | 51 | 33 | 23 |

The median length of follow-up in the treated group was also very much shorter: 0.3 years compared with 4.4 years in the conservatively managed group (Mann Whitney test, $p < 0.0001$). The two groups were similar with regard to sex ratio, lesion location and multiplicity.

### 9.2.3 Difficulties encountered when undertaking an individual patient data meta-analysis

#### Liaising with different study groups

Several challenges are encountered when undertaking an individual patient data meta-analysis, and the researcher must balance the requirement, on the one hand, of producing the meta-analysis within as short a time-period as is feasible, with the difficulties of trying to include the maximum number of studies, on the other. For example, a mean time of about 16 months elapsed between informal discussions about participating in the project to receipt of the datafile.

In an ideal situation, the project should be planned as a prospective study, with each research group following the same protocol, similar to a multi-centre trial. Unfortunately, however, this is an unrealistic scenario, especially for a study that is examining the clinical course of an uncommon disease, since the time required to

undertake such a study could be of the order of fifteen years and it would be prohibitively expensive. Therefore the researcher is forced to compromise and undertake a retrospective study, often using data that have been collected for a different purpose; as a consequence, this can restrict the scope of the project. Examples of this problem are the fact that focal neurological deficits were only recorded in three of the five cohorts, and the date of death was unavailable in another study.

It can be challenging and time-consuming for the coordinator of a meta-analysis to make sense of datasets from other research groups. In this study, for example, it was essential that definitions of intracranial haemorrhage and inception were the same among the studies to ensure that the same outcomes were being analysed. Fortunately, as a result of previous conflicting definitions of ICH and FND, a scientific workshop of the Angioma Alliance had been devoted to developing a consensus statement on the clinical and imaging features of CCM haemorrhage, and this subsequent definition and reporting guidelines were published in *Stroke* in 2008 (Al-Shahi Salman et al., 2008). The four studies in this meta-analysis all adhered to this definition.

Inevitably, a large amount of the researcher's time is spent liaising with different groups to clarify issues arising from the data, some of which will not be possible to resolve since the original researchers may no longer be working in the field or available to respond to queries, if several years or even decades have elapsed between the study being conceived and their data being used for a secondary purpose.

## 9.2.4 Other issues

### Age of data and neuro-imaging availability

The date of diagnosis for patients in the five cohorts in this study range over a period in excess of twenty years, from 1984 to 2011; about 50% were diagnosed before 2000. The patients in the two largest cohorts were diagnosed earlier, between 1984 and 1998 (Mayo Clinic, $n = 267$) and between 1987 and 2007 (Toronto, $n = 345$).

Although there has been a huge development in magnetic resonance imaging (MRI) techniques during this period, even in 1982–83 T1-weighted and T2-weighted spin-

echo sequences were available for use in the detection of cavernous malformations. T2 imaging sequences were used by Mayo Clinic (Kelly Flemming, personal communication). T2-weighted gradient-echo imaging (T2*GRE) is now considered to be the gold standard imaging sequence for detecting cavernous malformations, especially tiny lesions (Campbell et al., 2010, Lin and Abdalla, 2011), as it has increased sensitivity to haemorrhagic by-products. However, the length of time that has elapsed between the first patients in this study receiving a CCM diagnosis and the present day may not have had such a detrimental effect as might perhaps be envisaged. Nevertheless, it is possible that the neuro-imaging modalities available in the first years of this study were not sufficiently sensitive to detect an asymptomatic haemorrhage occurring during follow-up, which would be routinely detected if it were scanned now.

### Age as a predictor

As described in Chapters 6 and 8 above, the original intention had been to treat age as a continuous variable, to avoid unnecessary loss of information, power and precision (Royston et al., 2006). However, after testing the linearity assumption and discovering that it did not hold, it was necessary to treat age as a categorical variable.

Initially, Kaplan-Meier plots were produced with age split into three equal-sized groups; when the categorization was adjusted to enable the split to occur at a whole number, the log-rank test changed from being just statistically significant ($p = 0.048$) to non-significant ($p = 0.082$) for the unstratified five-cohort pooled analysis. To check whether this was an artefact, age was split into four categories; when the Kaplan-Meier plot was examined, no ordering was observed between the age-splits.

Univariate and multivariable analyses were undertaken twice, with age as both three- and four-category variables; in the meta-analysis age was treated as a continuous variable. However, regardless of whether it was treated as a categorical or continuous variable, there was no strong evidence of age adding any prognostic value to the model.

### Potential bias arising from observational studies

Unlike randomized controlled trials, observational studies are prone to bias and confounding (Hlatky et al., 1988, Byar, 1991, Riley et al., 2010). Nonetheless various methods were adopted in this meta-analysis to try to minimize potential problems of bias and confounding. First, pre-determined criteria for inclusion of studies, including minimum study size, patient eligibility, and definitions of inception and outcome events, were specified in the study protocol and statistical analysis plan.

Although there were difficulties acquiring data from previously published studies, which could lead to retrieval bias, at the time of informal discussion at the beginning of this project, only one study included in this meta-analysis had been previously published; indeed most of the data subsequently received from this study referred to patients who were diagnosed after the original study had been published, and therefore were not included in the original study. Thus at the start of this project the results of individual studies were unknown, and even when three of the studies were later published, the methods of statistical analysis differed and comparisons of results could not be made.

# Chapter 10: Concluding comments and future directions

## 10.1 Summary of results

Cerebral cavernous malformation is a challenging condition to study because it is not particularly common; the annual detection rate of a first-ever CCM was about 0.7 or 0.8 adults per 100,000 in Scotland in 2010. As a result of their angioarchitecture, CCMs are prone to bleed, and therefore an estimation of the risk of intracranial haemorrhage is of benefit to patients and clinicians alike. In this thesis, three investigations related to haemorrhage in follow-up have been conducted: the first two examined two cohorts of adults diagnosed with cerebral cavernous malformation that form part of the Scottish Intracranial Vascular Malformation Study (SIVMS), and the third is the five-cohort individual patient data meta-analysis.

In the first analysis, the risk of an intracranial haemorrhage or focal neurological deficit during untreated follow-up was investigated in both Scottish cohorts; in the second, functional and clinical outcome was compared between treated and conservatively managed adults in the earlier cohort (because there was insufficient follow-up in the later cohort to enable the analysis to be performed). Finally, the risk of an ICH (or a clinical event – either an ICH or FND) in untreated follow-up for adults from five international cohorts was investigated, risk factors for ICH (clinical event) were identified, and a prognostic model was built.

### 10.1.1 Outcome events in Scottish cohorts

In estimating the risk of an outcome event in the two Scottish cohorts (Chapter 4, (Al-Shahi Salman et al., 2012)), the risk was separated into two components: (i) the risk of a first outcome event (either ICH due to CCM or the composite outcome of ICH or FND, due or possibly due to CCM), for adults who presented with a seizure or incidentally, and (ii) the risk of a recurrent event, for adults who had already experienced a first event, whether at presentation or earlier in the follow-up period.

In each cohort, whether the outcome was intracranial haemorrhage definitely due to CCM or clinical event, due or possibly due to CCM, the risk of a recurrent outcome event was substantially greater than the risk of a first event: in the earlier cohort, the five-year risk of a recurrent haemorrhage was more than twelve times the five-year risk of a first bleed, and similarly the five-year risk of a recurrent clinical event was more than four times that of a first. Evidence from the first cohort suggested that women had a substantially greater risk of an outcome event within five years of presentation; this appeared biologically plausible, but it was not confirmed when the data from the second cohort were analysed two years later.

The level of dependency for adults from both cohorts who had experienced at least one ICH or FND was examined; the subgroups were divided into those who had suffered a single event and those who had suffered a recurrence. In each cohort, about 70% of adults who had suffered a single outcome event had a favourable outcome (OHS score 0–1), compared with about 40–55% of those who had experienced at least two events.

The strength of this investigation is that the study has been very carefully designed. It is a prospective population-based observational cohort study, which aimed to recruit all adults resident in Scotland, who had been diagnosed with a CCM that had been validated by MRI or by pathological examination within two five-year windows: between 1999 and 2003 (first cohort) and between 2006 and 2010 (second cohort). In addition to meticulous study design, data completeness for this analysis was very high.

Although the estimated risks are for the initial five years after presentation, in the first cohort follow-up was available for almost all participants for nine years.

Despite these strengths, however, there are a number of limitations. Cerebral cavernous malformation is not a common disease, and therefore the number of people diagnosed with the condition was small ($n$ = 141 and 166). Although it was possible to obtain an estimate for the risk of a first and a recurrent event, the precision of these estimates was poor. This was especially true for the recurrent risk, because the number of participants in each cohort who had experienced a first outcome – whether intracranial haemorrhage or clinical event – was very small, and consequently the number of outcome events (i.e. recurrent events) was even smaller.

To overcome these limitations, the sample size was increased by collaborating with three other research groups and conducting an individual patient data meta-analysis (Chapters 6–9, and subsection 10.1.3 below).

### 10.1.2 Comparison of outcome among treated and conservatively managed adults

In Chapter 5, the effect of treatment on both functional and clinical outcome was investigated in the earlier Scottish cohort (Moultrie et al., 2014). Adults in this observational study who underwent microsurgical CCM excision had a greater risk of sustained poor functional outcome in the first five years of follow-up than those who were conservatively managed. In addition, participants whose CCM had been excised had over three times the hazard of progression to either a first symptomatic intracranial haemorrhage or a new focal neurological deficit compared with individuals who did not undergo interventional treatment.

This analysis shares the same strengths with regard to meticulous study conduct as the first analysis; in addition, the fact that the treated group was being compared with a concurrent control group (conservative management) ensures that no temporal difference exists to influence the result. In this analysis, the limitation of comparatively few participants in each group is compounded by the fact that the study is an

observational design and the two groups were unbalanced at baseline (presentation). Statistical techniques – multivariable Cox regression – were used to adjust for baseline imbalances (age and mode of clinical presentation) and two other potential predictors (sex and brainstem location), but randomization of treatment allocation is the only effective method of ensuring that there is no systematic difference between the two groups before the treatment is started.

### 10.1.3 Individual patient data meta-analysis

In Chapters 6–9, an individual patient data meta-analysis is described, the aim of which was to improve the precision of previous estimated risks of ICH or clinical event in untreated follow-up and to identify prognostic factors. Almost one thousand adults from four different research centres were followed for five years, and two risk factors – ICH/FND presentation and brainstem location – were identified that are consistently associated with an increased likelihood of experiencing a haemorrhage or focal neurological deficit within five years of diagnosis. (In this analysis, date of diagnosis was taken as the inception point, whereas in the analysis of the two Scottish cohorts date of presentation was taken as inception.)

The Kaplan-Meier estimated risk of experiencing a first ICH within five years of diagnosis was 8.1% (95% CI 6.1% to 10.1%), and a first ICH or FND was 17.0% (95% CI 13.6% to 20.3%). Upon identification of the two prognostic factors, the pooled cohort was divided into four subgroups: those who possessed neither risk factor (i.e. presented with a seizure or incidentally, with a CCM located outside the brainstem) formed the lowest-risk, reference group and those with a brainstem CCM who presented with an ICH or FND were the highest-risk group. Adults who possessed a single risk factor had a similar level of risk, so these two groups were pooled in the final model (Model B), which thus consisted of no, one or two risk factors. The hazard that an adult with a single risk factor will suffer an ICH (clinical event) within five years of diagnosis is four (six) times that of an adult with no risk factors (see Table 10.1 (Table 8.17 from Chapter 8)). Similarly, the hazard for an adult with both risk factors is over fourteen times (eighteen times) that for an individual with none.

**Table 10.1 Model B: three-level prognostic model with hazard ratios and estimated five-year risk of outcome event**

| Risk factor | Adults | | ICH (ICH/FND) in 5-year follow-up | Hazard ratio | 95% confidence intervals | Estimate of five-year risk | 95% confidence intervals |
|---|---|---|---|---|---|---|---|
| | *n* | % | | | | | |
| **ICH only** | | | | | | | |
| Two risk factors | 173 | 18% | 36 | 14.3 | 7.1 to 28.8 | 25.7% | 18.3 to 33.2 |
| One risk factor | 249 | 25% | 16 | 4.0 | 1.8 to 8.7 | 9.5% | 4.9 to 14.1 |
| No risk factors | 566 | 57% | 10 | 1.0 | | 2.4% | 0.9 to 3.8 |
| **ICH or FND** | | | | | | | |
| Two risk factors | 113 | 18% | 48 | 18.0 | 9.4 to 34.8 | 50.7% | 40.1 to 61.4 |
| One risk factor | 172 | 27% | 29 | 6.1 | 3.1 to 12.2 | 22.3% | 14.8 to 29.8 |
| No risk factors | 355 | 56% | 11 | 1.0 | | 3.7% | 1.5 to 5.9 |

To my knowledge, this study is the largest investigation of haemorrhage risk in adults diagnosed with cerebral cavernous malformation. Data from five cohorts in four countries were cleaned and pooled into a single datafile, to enable the results to be synthesized in a meta-analysis. In addition to the number of participants, other strengths of this meta-analysis include the harmonization of definitions of outcome events, a common inception point, the completeness of baseline characteristics, the length of follow-up (five years), the ability to perform the same statistical techniques on each dataset, and the consistency in the direction and magnitude of the results, for both outcome events.

Limitations of the meta-analysis include the fact that not all of the eligible study groups initially identified and invited to collaborate were able to contribute data, as several had disbanded in the intervening years since publication of their results. Another weakness was that only three cohorts were able to supply data for focal neurological deficit; this was unfortunate because the effects of an FND can be equally as devastating to the patient as those of an ICH. However, this latter limitation is a consequence of using secondary data that were originally collected for a different purpose.

## 10.2 Future directions

As discussed in the previous section, the untreated clinical course of the disease has been explored both in two national cohorts and in a five-cohort meta-analysis. None the less, if further progress is to be made in the field, increased collaboration of research groups is needed so that a much larger dataset can be created. Following on from the current work, various directions that may be followed in the future are outlined below.

### 10.2.1 Validation of the prognostic model

As mentioned in the discussion of the individual patient data meta-analysis (Chapter 9), the prognostic model has not yet been validated. Although it is a very simple model, it has the advantage that both risk factors are available at time of diagnosis, and thus it has the potential to be used by clinicians at the appointment when the patient is given a CCM diagnosis. However, before it is used in clinical practice, it should be validated on an independent dataset (Altman and Royston, 2000).

### 10.2.2 CCM register

Although the following areas have not been discussed in this thesis, several pertinent clinical questions remain which have been tackled in the past with fairly small samples, but which would benefit from being addressed in a much larger population. Examples of such areas include whether antithrombotic therapy should be used with adults who have been diagnosed with a CCM, and the effect of pregnancy on women who have been diagnosed with a CCM. However, each question only affects a small proportion of the population diagnosed with a CCM; therefore an international register of people with a CCM diagnosis would be beneficial for answering some of these important questions that are of relevance to a substantial minority of individuals with CCM.

### 10.2.3 Comparison of treatment: a future trial?

In the analysis of treatment methods in Chapter 5, the problem of confounding by factors that were imbalanced at presentation and by two putative predictors was addressed to some extent by statistical methods. Nevertheless some bias will remain, since the allocation of patients to treatment group was determined by local clinicians, who were able to take various factors specific to each individual patient into consideration in an attempt to select what they considered to be the most appropriate

treatment choice, rather than by adults being randomly assigned to a treatment group, irrespective of their physical condition.

Thus long-term follow-up is required for the comparison of the effect of treatment on clinical and functional outcome, since it is possible that the risk of a clinical event in the conservatively managed group will continue to increase over time, although, based on the analysis in Chapter 4, this seems less likely. Additionally, CCM have been known to re-grow after surgery, and therefore it is possible that a de novo lesion might re-bleed.

Although there is a second Scottish cohort upon which the analysis of functional outcome among different treatment groups can be performed (and the results of this analysis can be compared to the earlier cohort), analysis of the later cohort will have the same major flaw as the first cohort – namely lack of randomization. In addition, if the same follow-up criteria are adhered to – a five-year window after presentation for interventional treatment to take place, and then five years for follow-up for those who underwent interventional treatment – analysis of the second cohort would not be possible until after 2020!

The investigation in Chapter 5 paves the way for a randomized controlled trial (RCT). From a methodological perspective, a randomized controlled trial is required in the future to give a definitive answer to the question of the impact of intervention on the course of the disease. The random allocation of sufficient numbers of patients to each treatment strategy will ensure that potential confounding factors are equally distributed in the treatment groups. In addition, eligibility criteria can be pre-specified in the protocol so that participants who have, for example, multiple comorbidities, and are thus likely to have a poor outcome due to health problems other than CCM, can be excluded from recruitment to the trial.

From a clinical point of view, there is a paucity of well-conducted studies comparing patient outcome after different methods of treatment (Recinos et al., 2011, von der Brelie and Schramm, 2011, Menon et al., 2011, Berg and Vay, 2011, Poorthuis et al., 2013, Poorthuis et al., 2014). In particular, several studies report outcomes of treatment undertaken over fifteen years ago, which are probably outdated, since neuro-imaging

techniques and neuro-navigation have become more sophisticated, and neurosurgical, stereotactic radiosurgery methods and electrophysiological monitoring have developed in the intervening period.

However, although a randomized controlled trial is the optimum study design, the omens for such a trial are not auspicious: a similar RCT was initiated among eight neurovascular research groups in North America, under the leadership of a neurological surgery research group at the University of Pittsburgh, several years ago, but was abandoned after a year, because no participants had been recruited (see Kondziolka and Lunsford's response to Steiner (Steiner et al., 2010)). Nevertheless recruitment to the abandoned trial was confined to patients with cavernous malformations in 'high-risk' locations, and to eight research centres in North America and Canada, and compared surgical resection with radiosurgery. A future trial would need to be more inclusive, both in terms of its patients and the geographical location of research centres.

It is understandable that recruitment of participants to a treatment RCT would be challenging: although CCMs are not uncommon, recruitment would be restricted to participants where the clinician was in a genuine state of clinical equipoise and the patient was willing to be allocated to one of two or three (if stereotactic radiosurgery were included) treatments randomly. In practice, recruitment would be restricted to adults with at least one risk factor, since individuals with no risk factors would almost certainly be unwilling to risk the potentially harmful effects of surgery when their estimated risk of a future haemorrhage within five years of CCM diagnosis was 2.4% (95% CI 0.9% to 3.8%) (estimated five-year risk of clinical event: 3.7% (95% CI 1.5% to 5.9%)). However, widening the inclusion criteria to patients with a cerebral cavernous malformation in any location, and extending the invitation to participate to large centres in other parts of the world may result in a more successful venture.

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# Appendices

# Appendix A: Statistical Analysis Plan for Chapter 5

## Functional outcome after surgery or conservative management

I Baseline Characteristics

- Total adults with CCM (*n* = 160)
  - probable/possible (*n* = 21) – Not_definite_CCM.xls
  - definite (*n* = 139) – Definite_CCM_1_patient_row_prim_loc.sav
    - diagnosed at autopsy (*n* = 5) – include description in 'Methods' text, but not in tables, as they do not contribute to follow-up
    - surgery (*n* = 25)
    - conservatively managed (*n* = 109)
      - Predictors of interest – Baseline_characteristics.sav
        - Age at start of follow-up (or treatment)*†
        - Sex*
        - CCM: single or multiple
        - Location*†
          - symptomatic CCM; or
          - if asymptomatic and multiple including a brainstem CCM, then location = brainstem.

            Multivariate analysis will be brainstem *vs* other location.
          - Brainstem = PONS, MEDUL, MIDB (3)
          - Deep = CHOR, THAL, BGANG (2)
          - Cerebellum = CEREBE (1)
          - Lobar = *all other* (4)
        - Mode of clinical presentation*†
          - epileptic seizure (E)

- intracranial haemorrhage (ICH)(Al-Shahi Salman et al., 2008)
- focal neurological deficit (FND)(Al-Shahi Salman et al., 2008):
  - non-haemorrhagic FND = NHFTR, NHFPE or NHFPR
  - FND not otherwise specified = FNDTR, FNDPE or FNDPR
- incidental (A):
  - if patient was asymptomatic; or
  - if symptoms could not be attributed – definitely or possibly - to the underlying CCM.

Multivariate analysis will be ICH or FND at presentation *vs* A or E at presentation
Where an individual who later has interventional treatment presents incidentally or with a seizure, but then experiences an ICH or FND due to the CCM or unknown cause in the period ***between*** *presentation and intervention*, the mode of clinical presentation will be recoded to the last clinical event experienced in untreated prospective follow-up and the date of presentation will be changed to the date of first clinical event (also, the CCM location may be recoded, if this is appropriate).

**Pre-specified for adjustment of hazard ratios and multivariate analyses*

†*May vary according to whether analyses are pre- or post-treatment for the treated group.*

## II Completeness of follow-up

- Entire cohort: from presentation date, all follow-up, until death of any cause or last available follow-up, analysed in February 2011:
  MH_CCM_1stCoh_Presentatn_Untx_Follup_8_outcomes_completeness.xlsx
  MH_CCM_1stCoh_Presentatn_Untx_Follup_8_outcomes_completeness.sav
- Total = 1,177 person-years actual (of 1,216 potential person-years)
- Using the Clark *et al*. method = 97% completeness

III Outcome Analyses

- ***Included patients:*** definite CCM and alive at presentation date ($n$ = 134), since the five adults who were diagnosed at autopsy do not contribute any follow-up (the latter will be described in the 'Methods' section, however)

- ***Period at risk***
  - **'untreated follow-up':**
    - all available follow-up from date of first presentation until outcome event or censoring at 5 years for those adults who did not have an intervention; or
    - all available follow-up from date of first presentation until date of first intervention; and
  - **'treated follow-up':** all available follow-up from date of first intervention until outcome event or censoring at 5 years after intervention.

  **Censoring** took place at the earliest occurrence of any of the following: death unrelated to CCM; last available follow-up; 5 years after initial presentation (conservatively managed group); or 5 years after first CCM intervention (treated group).

- ***Treatment:*** CCM surgical excision/radiosurgery that was performed and treated the CCM.

- ***Outcome event rates***
  - **Functional outcome:** sustained deterioration, measured from the date of the first of two consecutive OHS scores of 2-6, occurring within 5 years of the start of follow-up (*after presentation* for the conservatively managed group and *after first intervention* for the treated group) (Kaplan-Meier survival analysis and life tables)

- **Events:** first occurrence of ICH/FND/infarction due to CCM, unknown, or intervention after the start of follow-up

- ***Univariate analyses***
  - **Baseline characteristics**
    - Compare baseline characteristics, treated *vs* conservatively managed

      Use: MH_CCM_1stCoh_134_Untx_Tx.sav (*n* = 134)
  - **Functional outcome** – *primary outcome*
    - Compare hazard ratio for functional outcome, treated (*after intervention* date) *vs* conservatively managed (*after presentation*) over 5 years

      Use: MH_CCM_1stCoh_134_Untx_Tx.sav (*n* = 134, OHS scores adjusted for treated adults)
  - **Clinical events** – *explanatory secondary outcome measure*
    - Describe **untreated** clinical course in the treated group – i.e. number of people who experience ICH or FND, due to CCM or unknown cause, *before* they receive interventional treatment (*between presentation and intervention dates*)

      Use: MH_CCM_1stCoh_post_pres_8_outcomes_25.sav (*n* = 25)
    - Compare hazard ratio for time to first clinical event (ICH, CI or FND, due to CCM, unknown cause or surgical procedure), treated group (*after first intervention*) *vs* conservatively managed group (*after presentation*) over 5 years

      Use:

      MH_CCM_1stCoh_134_Untx_Pres_Treated_Post_Tx.sav

      (*n* = 134)
    - Describe deaths (and their causes) within 30 days of treatment

      Use: MH_CCM_1stCoh_134_Untx_Tx.sav (*n* = 134) + SAIVMS Live database

- ***Adjustment of hazard ratios:*** for primary and secondary outcomes, adjust by factors imbalanced at baseline (age and mode of presentation) and known to influence CCM prognosis (CCM primary location and sex)

- ***Multivariate analyses:*** outcomes *after presentation / intervention date,* censored at 5 years (Cox proportional hazards, provided assumptions fulfilled)
    - We will examine each of the following predictors in the primary and secondary analyses, and the number entered will depend on the number of outcome events (10 events per variable), but they will be chosen in the following order:
        - age at presentation
        - mode of clinical presentation
        - CCM location
        - sex

    Use: MH_CCM_1stCoh_134_Untx_Tx.sav (*n* = 134)
    MH_CCM_1stCoh_134_Untx_Presx_Treated_Post_Tx.sav (*n* = 134)

## Reference

AL-SHAHI SALMAN, R., BERG, M.J., MORRISON, L., AWAD, I.A., on behalf of the Angioma Alliance Scientific Advisory Board. Haemorrhage from cavernous malformations of the brain: definition and reporting standards. *Stroke*. 2008; 39(12): 3222-30.

# Appendix B: Summary Protocol for IPDMA

## Untreated Clinical Course of Cerebral Cavernous Malformations: an individual patient data meta-analysis

Margaret Horne[1], Ronit Agid[2], Kelly D. Flemming[3], Robert D. Brown, Jr[3], Teresa Christianson[3], Karel G. terBrugge[2], Robert Willinsky[2], I-Chang Su[2], Christian Stapf[5], Gordon Murray[1] and Rustam Al-Shahi Salman[4]

Institutions

[1]*Centre for Population Health Sciences, University of Edinburgh, UK*

[2]*Division of Neuroradiology, Department of Medical Imaging, Toronto Western Hospital, Toronto, Ontario, Canada*

[3]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*

[4]*Division of Clinical Neurosciences, Centre for Clinical Brain Sciences, University of Edinburgh, UK*

[5] *Acute Neurovascular Unit, Hôpital Lariboisière, Paris, France*

### Research problem

Publications from the Scottish Intracranial Vascular Malformation Study (SIVMS, www.saivms.scot.nhs.uk),[1] the Mayo Clinic (www.mayoclinic.org/central-nervous-system-vascular-malformations/),[2] the Toronto Brain Vascular Malformations Study Group (http://brainavm.oci.utoronto.ca/)[3] and others (Figure) constitute the best knowledge available about the prospective risks of intracranial haemorrhage and non-haemorrhagic focal neurological deficits in patients with cerebral cavernous malformations (CCM). These papers also identify risk factors for symptomatic events. However, as pointed out in accompanying editorials,[4, 5] there remain important

uncertainties regarding the natural history of people with untreated CCM. All published studies to date have been based on relatively small sample sizes, so that even when risk factors are identified consistently (e.g. the importance of a prior haemorrhage in determining the risk of a future haemorrhage), the magnitude of the effect has not been estimated with precision. For other putative risk factors (e.g. patient sex or the location of the CCM), the literature is inconsistent.

We propose an individual patient data meta-analysis of the prognosis of untreated CCM to address these outstanding uncertainties. By pooling data from several large studies, we shall be able to quantify known risks with much greater precision and develop a consensus over putative risk factors. Ultimately we shall develop and evaluate/validate a prognostic model based on several covariates. Although not a specific aim of the first phase of this collaboration, the exercise of assembling the data from several cohorts will also allow us to assess whether it would be feasible to address some even more challenging questions, including the impact of pregnancy and antithrombotic drugs on the risk of clinical events, and to identify risk factors derived from imaging.

### *Challenges*

The precise research questions which can be addressed will depend on many factors, including the variation in the design of the different constituent studies (for example, at what point in their clinical course patients were recruited into the study; whether follow-up time can be split as pre-treatment and post-treatment, where applicable; and what systems are in place for follow-up), and the types of events (whether any symptomatic neurological events were recorded or only haemorrhagic events, and whether these events are confirmed by brain imaging). Equally, the statistical power of our analyses will be limited by the number of outcome events that can be included; this will also shape the research questions that can be addressed.

### *Approach*

We plan, therefore, to adopt a two-step approach to the project. In a first exploratory phase, we shall identify collaborators, gather background information on the relevant

study designs and databases, and accumulate the data centrally. In the second phase, we shall refine the scientific protocol, based around the practical constraints of what research questions can be addressed, given the strengths and limitations of the assembled data, with the input of our collaborators. To avoid the perception that the analysis is 'data driven' we set out the primary and secondary objectives below, although we recognise that the detailed scientific protocol can only be finalised in the light of the results of the first phase of the work.

The intention is to complete as much as is possible of the first phase in time to inform discussions at the first investigator meeting to be held in Edinburgh in September 2012, around the time of the AVM Conference (18-19 September) or ESNR Annual Meeting (20-23 September).

## Objectives

### *Primary Objectives*

- *Descriptive analysis of time-to-event outcomes.* Outcomes during untreated follow-up will include intracranial haemorrhage (ICH), but also focal neurological deficit (FND) or a composite endpoint of ICH or FND, if the data have been recorded in such a way as to permit this. In addition, we will examine event rates over long periods of follow-up to ascertain whether the estimated risk remains constant, or whether it diminishes over several years.
- *Identification of risk factors.* In most studies a prior ICH has been identified as a risk factor for a future ICH, but the magnitude of this effect is uncertain; sex, CCM location, and possibly age are the other putative risk factors, which we will examine if there is sufficient power (i.e. enough outcome events).
- *Building and evaluating a multivariate prognostic model.* The model will be used to predict the probability of a future ICH (± FND, if the data are available) for an adult with CCM(s) during untreated follow-up. Pre-specified covariates

in the model will be chosen for clinical significance and will include prior ICH/FND, sex, CCM location and possibly age.

### *Secondary Objective*

- *Exploring potential for future work.* For example, what is the effect of pregnancy on the untreated course of the disease; what is the effect of antithrombotic therapy on adults with untreated CCM; does CCM size influence disease outcome; how does treatment (with neurosurgical excision or stereotactic radiosurgery) affect outcome?

## Methods

### *Eligibility criteria for study cohorts*

- Each study should have a minimum sample size of 60 adults.
- Period at risk should begin at either (i) first CCM diagnosis ('date of diagnosis'), or (ii) symptoms leading to it ('date of clinical presentation'), thereby enabling calculation of event risk (not retrospective 'lifetime risk') at standardised time-points in the disease course.
- ICH should be included as an objective pre-defined clinical outcome.
- Outcome events should be able to be quantified per patient during the follow-up period.

### *Eligibility criteria for patients within study cohorts*

- Adults who have received a first-ever CCM diagnosis.
- Diagnosis validated either by brain MRI or pathological examination.
- Patients to have some untreated follow-up time to contribute to the study.

### *Types of outcome measures*

Although ICH is the primary outcome measure in this study, it is important to include in our analysis, wherever possible, adults who suffer non-haemorrhagic FNDs – either as a separate outcome measure, or as a secondary composite endpoint. Both ICH and FND have a similar level of severity for the patient, and in certain circumstances an outcome labelled FND may, in reality, be an ICH, but not categorised as such, either because the appropriate neuro-imaging was not performed or because the imaging failed to detect any blood.[6]

## Analysis

In this study, our sole interest is the **untreated** course of the disease: thus adults who have received some form of interventional treatment will contribute data to the survival analyses only until the date of first treatment, at which point their data will be censored. Data will be censored at the earliest occurrence of any of the following: death unrelated to CCM; treatment (whether surgery or stereotactic radiotherapy); last available follow-up.

Fundamentally, we will perform analyses within studies and pool the results (e.g. an estimated hazard ratio or an estimated adjusted hazard ratio) using forest plots and random effects meta-analysis.

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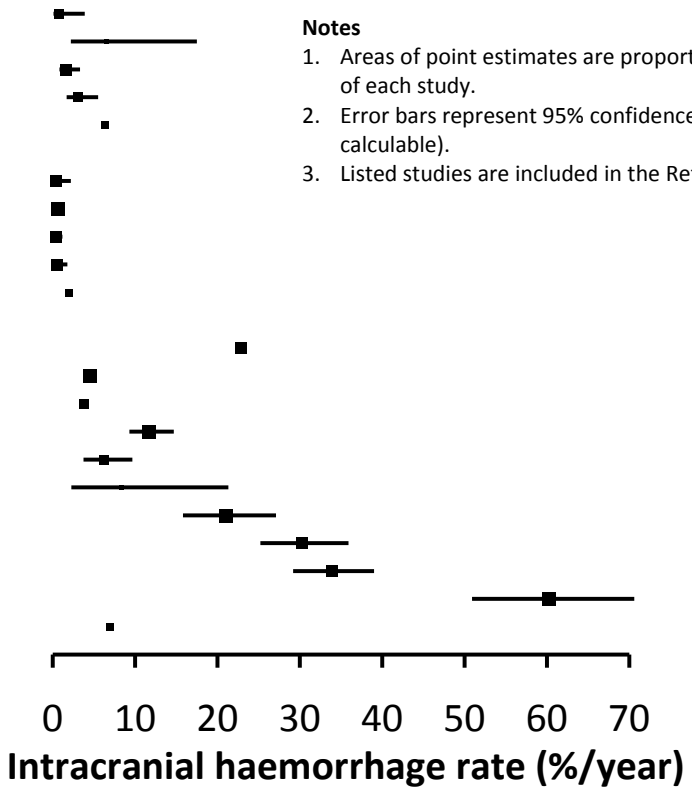
**Figure 1 Risk of symptomatic intracranial haemorrhage during follow-up in studies of the untreated clinical course of > 20 participants with cerebral cavernous malformations**

| Study | Selection criteria | Sample size | Mean follow-up (yrs) |
|---|---|---|---|
| **First/recurrent intracranial haemorrhage not distinguished** | | | |
| Robinson *et al.* 1991 | None | 66 | 2·2 |
| Zabramski *et al.* 1994 | Familial | 21 | 2·2 |
| Porter *et al.* 1997 | None | 110 | 3·8 |
| Moriarity *et al.* 1999 | None | 68 | 5·2 |
| Ghannane *et al.* 2007 | None | 39 | 2·5 |
| **First intracranial haemorrhage** | | | |
| Aiba *et al.* 1995 | None | 110 | 4·7 |
| Kondziolka *et al.* 1995 | None | 122 | 2·8 |
| Flemming *et al.* 2012 | None | 108 | 7·3 |
| Al-Shahi Salman *et al.* 2012 | None | 96 | 5·0 |
| Mathiesen *et al.* 2003 | Brainstem and deep | 34 | 4·6 |
| **Recurrent intracranial haemorrhage** | | | |
| Aiba *et al.* 1995 | None | 110 | 4·7 |
| Kondziolka *et al.* 1995 | None | 122 | 2·8 |
| Kim *et al.* 1997 | None | 62 | 1·9 |
| Barker *et al.* 2001 | None | 136 | 3·8 |
| Flemming *et al.* 2012 | None | 74 | 7·3 |
| Al-Shahi Salman *et al.* 2012 | None | 18 | 5·0 |
| Fritschi *et al.* 1994 | Brainstem | 139 | 2·5 |
| Porter *et al.* 1999 | Brainstem | 100 | 2·0 |
| Hasegawa *et al.* 2002 | Brainstem | 83 | 4·3 |
| Wang *et al.* 2003 | Brainstem | 137 | 1·8 |
| Mathiesen *et al.* 2003 | Brainstem and deep | 34 | 4·6 |




**Notes**

1. Areas of point estimates are proportional to the sample size of each study.
2. Error bars represent 95% confidence intervals (if available or calculable).
3. Listed studies are included in the References (1-2, 5-18).

# Appendix C: Letter of invitation to join the IPDMA and initial questionnaire

DIVISION *of* CLINICAL NEUROSCIENCES

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Dr *Name*

*Address*

21 March 2012

Dear

**Collaborative individual patient data meta-analysis of cerebral cavernous malformation prognosis**

I am writing in the hope that you will contribute to an individual patient data meta-analysis of the prognosis of cerebral cavernous malformations (CCM). At present, this collaborative endeavour involves the Scottish Intracranial Vascular Malformation Study (SIVMS, a population-based cohort of ~300 adults with CCM),[1] the Mayo Clinic (a hospital-based cohort of ~300 patients with CCM),[2] and the Toronto Brain

[1] Al-Shahi Salman R *et al.* Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study. *Lancet Neurol* 2012; 11: 217-224.

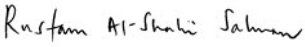
[2] Flemming KD *et al.* Prospective hemorrhage risk of intracerebral cavernous malformations. *Neurology* 2012; 78: 632-6.

Vascular Malformation Study Group (a hospital-based cohort of ~800 patients with CCM).[3] Your work is one of sixteen published series that we have identified by systematically reviewing the literature on the **untreated outcome** for people with CCM.[4] Although all of these studies have provided valuable information regarding the natural history of CCM, there would be several potential benefits of a large collaboration: the precision of the estimated risks of first and recurrent intracranial haemorrhage (and/or focal neurological deficit) could be improved, some inconsistent findings in the literature (for example, the influence of patient sex and CCM location on prognosis) could be re-examined, as well as others such as the influences of pregnancy and antithrombotic drugs, and a prognostic model with several covariates could be developed and validated.

Looking ahead to publication, you would need to provide your data by the beginning of September 2012. We hope to have our first meeting of the CCM collaboration soon afterwards at the 1st World AVM Congress in Edinburgh on 18-19 September 2012 (www.avm2012.org). The paper will include core authors from each group that contributes data; other members of the contributing research groups will be listed as collaborators (for further details see www.nlm.nih.gov/pubs/techbull/ma08/ma08_collaborators.html).

Please could you let me know whether you will join us by completing and sending me the attached form **by Thursday 12 April 2012**?

With best wishes



**Dr Rustam Al-Shahi Salman** MA PhD FRCP Edin
*MRC Senior clinical fellow, University of Edinburgh*
*Honorary consultant neurologist, NHS Lothian*

**Professor Gordon D. Murray** PhD FRCP Edin FRSE
*Professor of Medical Statistics,*
*University of Edinburgh*

---

[3] Porter PJ *et al.* Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. *J Neurosurg* 1997; 87: 190-7

[4] *Collaborator's work*

**Your name:**

**Your study:**

**Please ✓ one answer to each question:**

1. **Do you still have the original dataset from your publication about CCM?** **Yes** ☐ **No** ☐

**→ If 'No', stop**

2. **If 'yes' to question 1, will you share data with this meta-analysis?** **Yes** ☐ **No** ☐
3. **If 'yes' to question 2, is this dataset stored electronically?** **Yes** ☐ **No** ☐
4. **Do you have copies of the CCM patients' brain imaging?** **Yes** ☐ **No** ☐
5. **Please could you provide the following details about the design of your study?**

   a. **At what time does follow-up start?** **✓ all that apply**

   - First ever symptom that might have been due to CCM ☐
   - Clinical presentation that led to CCM diagnosis ☐
   - Time of referral to your service/hospital for consultation ☐
   - Time of referral to your service/hospital for CCM treatment ☐

   b. **How do you follow-up patients?** **✓ all that apply**

   - Only when they are admitted to hospital attend a clinic appointment ☐
   - General (family) practitioners ☐
   - Patient telephone calls ☐
   - Patient postal questionnaires ☐
   - Death records ☐

   c. **Which outcome events do you record?** **✓ all that apply**

   - Death ☐
   - CCM haemorrhage, confirmed by review of brain imaging ☐
   - CCM haemorrhage, based on reports of brain imaging by others ☐
   - Focal neurological deficits, where brain imaging has been performed ☐
   - Focal neurological deficits, where brain imaging has <u>not</u> been performed ☐

6. **Please provide the name and email of your data manager, statistician, or equivalent colleague:**

# Appendix D: Questionnaires for IPDMA collaborators

## I Clinical questionnaire for Kelly Flemming (Mayo Clinic)

**Please ✓ one answer to each question**

1. If your patients have received treatment, can you divide follow-up for each patient into:

   - before treatment — Yes ☐ No ☐
   - after treatment — Yes ☐ No ☐

2. Does follow-up begin at the same point – the clinical presentation that led to CCM diagnosis – for **all** patients? — Yes ☐ No ☐

3. You said in the previous questionnaire that follow-up was completed around 2003, apart from those patients who presented asymptomatically. Would it be possible to update follow-up on **all** patients? — Yes ☐ No ☐

4. Please can you give us more details about how you organize follow-up. Is it organized:

   - at regular intervals for **all** patients? — Yes ☐ No ☐
   - irregularly, depending on each patient's clinical status? — Yes ☐ No ☐

5. If follow-up is at regular intervals, please could you specify the frequency.

| |
|---|
| |

Please return by email: rustam.al-shahi@ed.ac.uk or fax: +44 131 332 5150

# II Statistical Questionnaire for the Mayo Clinic study

**Please answer the following questions.**

1. How many patients in your CCM cohort are available for follow-up analysis? ☐

2. In the first questionnaire, you indicated that you record death, intracranial haemorrhage (ICH) and non-haemorrhagic focal neurological deficit (FND). How many people in your study have had, **in follow-up**:

   - at least one ICH? ☐
   - one or more FND? ☐
   - have died? ☐

**Please ✓ one answer to each question**

3. Is a data dictionary available for your dataset? Yes ☐ No ☐

4. What data are you able to send us:

   - all clinical events and total duration of follow-up for each patient? Yes ☐ No ☐
   - first events only, and the duration of follow-up to that point? Yes ☐ No ☐

5. In what format are you able to share your data?

☐

**Please ✓ one answer to each question**

6. What dataset will you share with us:

   - a copy of one previously used for a publication analysis? Yes ☐ No ☐
   - a recent extract from your database? Yes ☐ No ☐

Please return by email: rustam.al-shahi@ed.ac.uk or fax: +44 131 332 5150

# III Clinical Questionnaire for the Toronto study

In questions 1 and 2, please could you clarify when follow-up begins in your study. In the previous questionnaire, you indicated that it started at three different time-points – first-ever symptom that might have been due to CCM; clinical presentation that led to CCM diagnosis; and time of referral to your hospital for CCM treatment.

**Please ✓ one answer to each question**

1. Do you have information about
   - the date and — Yes ☐ No ☐
   - the mode of clinical presentation that led to CCM diagnosis — Yes ☐ No ☐

   for **all** patients in your study?

2. If 'No', please can you specify the approximate number / percentage of the cohort included at each time-point.
   - first-ever symptom that might have been due to CCM ☐
   - clinical presentation that led to CCM diagnosis ☐
   - time of referral to your hospital for consultation ☐

3. You did not record death as an outcome event in the previous questionnaire. Do you know each patient's vital status at the end of follow-up? Yes ☐ No ☐

4. If your patients have received treatment, can you divide follow-up for each patient into:
   - before treatment — Yes ☐ No ☐
   - after treatment — Yes ☐ No ☐

5. You have said that follow-up occurs when patients are admitted to hospital or attend a clinic appointment. Is follow-up organized at:
   - regular intervals for **all** patients? — Yes ☐ No ☐
   - irregularly, depending on each patient's clinical status? — Yes ☐ No ☐

6. If follow-up is at regular intervals, please could you specify the frequency.

Please return by email: rustam.al-shahi@ed.ac.uk or fax: +44 131 332 5150

# IV Statistical Questionnaire for the Toronto study

**Please answer the following questions.**

1. How many patients in your CCM cohort are available for follow-up analysis? ☐

2. In the first questionnaire, you indicated that you record intracranial haemorrhage (ICH) and non-haemorrhagic focal neurological deficit (FND). How many people in your study have had, **in follow-up**:

   - at least one ICH? ☐
   - one or more FND? ☐

**Please ✓ one answer to each question**

3. Is a data dictionary available for your dataset? Yes ☐ No ☐

4. What data are you able to send us:

   - all clinical events and total duration of follow-up for each patient? Yes ☐ No ☐
   - first events only, and the duration of follow-up to that point? Yes ☐ No ☐

5. In what format are you able to share your data?

☐

**Please ✓ one answer to each question**

6. What dataset will you share with us:

   - a copy of one previously used for a publication analysis? Yes ☐ No ☐
   - a recent extract from your database? Yes ☐ No ☐

Please return by email: rustam.al-shahi@ed.ac.uk or fax: +44 131 332 5150

# V Clinical questionnaire for Christian Stapf (Paris)

In questions 1 and 2, please could you clarify when follow-up begins in your study. In the previous questionnaire, you indicated that it started at three different time-points – first-ever symptom that might have been due to CCM; clinical presentation that led to CCM diagnosis; and time of referral to your hospital for CCM treatment.

**Please ✓ one answer to each question**

1. Do you have information about
   - the date and — Yes ☐ No ☐
   - the mode of clinical presentation that led to CCM diagnosis — Yes ☐ No ☐

   for **all** patients in your study?

2. If 'No', please can you specify the approximate number / percentage of the cohort included at each time-point:
   - first-ever symptom that might have been due to CCM ☐
   - clinical presentation that led to CCM diagnosis ☐
   - time of referral to your hospital for consultation ☐

3. If your patients have received treatment, can you divide follow-up for each patient into:
   - before treatment — Yes ☐ No ☐
   - after treatment — Yes ☐ No ☐

4. You have said that patients are contacted at regular intervals by telephone. Please can you specify:
   (i) whether this happens for **all** patients and
   (ii) the frequency of the follow-up.

☐

Please return by email: rustam.al-shahi@ed.ac.uk or fax: +44 131 332 5150

# VI Statistical questionnaire for the Paris study

**Please answer the following questions.**

1. How many patients in your CCM cohort are available for follow-up analysis? ☐

2. In the first questionnaire, you indicated that you record death, intracranial haemorrhage (ICH) and non-haemorrhagic focal neurological deficit (FND). How many people in your study have had, **in follow-up**:

   - at least one ICH? ☐
   - one or more FND? ☐
   - or have died? ☐

**Please ✓ one answer to each question**

3. Is a data dictionary available for your dataset? Yes ☐ No ☐

4. What data are you able to send us:

   all clinical events and total duration of follow-up for each patient? Yes ☐ No ☐

   - first events only, and the duration of follow-up to that point? Yes ☐ No ☐

5. In what format are you able to share your data?

| |
|---|
| |

**Please ✓ one answer to each question**

6. What dataset will you share with us:

   a copy of one previously used for a publication analysis? Yes ☐ No ☐

   a recent extract from your database? Yes ☐ No ☐

Please return by email: rustam.al-shahi@ed.ac.uk or fax: +44 131 332 5150

# Appendix E: Statistical Analysis Plan for IPDMA

## Clinical course of untreated cerebral cavernous malformations: an individual patient data meta-analysis

### Background

#### *The disease*

A cerebral cavernous malformation (CCM) is a small round cluster of thin-walled, dilated blood vessels, packed together with no intervening brain tissue. As a result of their angioarchitecture, CCM are prone to bleed. Although the quantity of blood leaking out tends to be small because the blood flow is very slow, even a small intracranial haemorrhage (ICH) can result in a clinically significant neurological deficit, especially when the CCM is located in the brainstem or another eloquent area.

CCM detection has increased alongside greater use of brain magnetic resonance imaging (MRI) (Brown et al., 1996, Al-Shahi et al., 2003). In particular, this can lead to many asymptomatic CCM being detected since the prevalence of CCMs is 0.16–0.39% of the population (Morris et al., 2009, Del Curling et al., 1991). The magnitude and predictors of the risk of ICH in the clinical course of untreated CCM are important to patients and clinicians because estimates of prognosis inform decisions about whether to treat CCM.

CCMs constitute a challenging condition to study. The diagnosis may be subject to detection bias, since it relies on brain imaging of the right type being performed at the right time, and clinicians tend to investigate the cause of ICH in young, normotensive adults, whereas ICH in older, hypertensive adults is less likely to be further investigated. If patients with CCM who are treated conservatively have minor symptoms they may be less likely to report them (if they know they will not be treated, and their clinicians in turn may be less likely to arrange radiographic investigation) or more likely to report them (if they are anxious for the treatment decision to be changed). Therefore, because some new focal neurological deficits (FND) may have

been undetected ICHs, reporting standards recommend combining proven ICH and FND into a composite outcome (Porter et al., 1997, Al-Shahi Salman et al., 2012).

### *Risk of intracranial haemorrhage from CCM*

Several studies have described the risk of ICH in the clinical course of untreated CCM (Al-Shahi Salman et al., 2012, Flemming et al., 2012, Flemming et al., 2013, Schneble et al., 2012). However, the main limitations of these studies have been small sample size and short follow-up. Most of these studies were retrospective hospital-based series, without clearly-defined diagnostic criteria or outcome events (Al-Shahi Salman et al., 2008), and some restrict inclusion to selected participants according to the anatomical location of the CCM or whether its cause is genetic/sporadic.

Comparison of the risks of ICH between these studies is problematic because different statistical methods have been used to calculate risk. In many papers, authors have calculated the risk of ICH assuming that the CCM is congenital, whereas it is now accepted that lesions do occur *de novo* during lifetime (Zabramski et al., 1994, Kattapong et al., 1995, Detwiler et al., 1997). In some studies, the risk per lesion has been estimated rather than that per patient. In other studies, the total number of ICHs in follow-up rather than the first ICH in follow-up was used to calculate an annual rate, and it was also assumed that the annual rate is constant over time, which appears not to be the case (Barker II et al., 2001, Al-Shahi Salman et al., 2012). Overall, the annual rates of first-ever ICH (0.3% to 1.3%) have been lower than recurrent ICH (6.2% to 18.3%) from the same CCM, but neither of these rates has been estimated with precision (Al-Shahi Salman et al., 2012, Flemming et al., 2012).

### *Predictors of intracranial haemorrhage from CCM*

Most studies have consistently identified the occurrence of a prior ICH as a risk factor for an adult developing a subsequent ICH. Studies have varied in whether putative risk factors such as patient sex, CCM location or CCM multiplicity have influenced the risk of ICH.

Therefore, the patient's and clinician's dilemma about whether, when, and how to treat a CCM would be informed by a more precise estimation of the clinical course of

untreated CCMs, the identification of prognostic factors, and the derivation and validation of a prognostic model.

## This collaborative individual patient data meta-analysis

After conducting a systematic review (Al-Shahi Salman et al., 2012), we identified five cohorts of adults with CCM that could provide detailed individual patient data regarding clinical outcome (ICH or FND) between diagnosis and either CCM treatment or last follow-up. By conducting an individual patient data meta-analysis(Riley et al., 2010), we will be able to use consistent methods of analysis for all patients across studies and investigate two outcomes: ICH alone and a composite outcome of ICH and new FND. We aim to improve the precision of previous estimated risks of first and recurrent ICH (and also the composite outcome of first or recurrent ICH or FND), and identify prognostic factors for ICH/FND. We will also develop and evaluate/validate a prognostic model based on several covariates. In exploratory subgroup analyses, we will assess whether it would be feasible in the future to examine the impact of antithrombotic drugs on the risk of ICH/FNDs and to identify risk factors derived from neuro-imaging.

### *Study questions*

1. What is the estimated risk of an untreated adult suffering an ICH or FND within five years of CCM diagnosis?
2. Which baseline characteristics modify the risk of ICH or FND occurring within five years of CCM diagnosis?
3. Is it possible to predict, at the time of diagnosis, an individual's risk of a subsequent ICH or FND?

### *Study design*

This is a two-stage random-effects individual patient data meta-analysis in which the unadjusted and adjusted hazard ratios will be derived for each cohort, and summary adjusted hazard ratios will be calculated, if this is appropriate (Riley et al., 2011).

### *Study cohorts*

#### *Eligibility criteria*

- Each study should have a minimum sample size of 60 adults.
- The period at risk should begin at either
  (i) first CCM diagnosis or
  (ii) symptoms leading to it
  thereby enabling calculation of event risk from diagnosis (not retrospective 'lifetime risk').
- Symptomatic ICH should be included as an objective, pre-defined clinical outcome.
- Outcome events should be able to be quantified per patient during the follow-up period.

Data will be used from five cohorts: two cohorts that were recruited at different five-year time periods in the same prospective, population-based observational study (Al-Shahi Salman et al., 2012), and three hospital-based cohorts (Porter et al., 1997, Flemming et al., 2012b, Schneble et al., 2012a).

### *Participant eligibility*

#### *Inclusion criteria*

- Participants with a definite CCM diagnosis.
- Diagnosis validated either by MRI or pathological examination after surgical excision.
- Participants should be aged 16 years or over at time of diagnosis.

- Participants should not have received interventional treatment – surgical excision or stereotactic radiotherapy – by the time of diagnosis.

*Exclusion criteria*

- Any adult in a cohort who was diagnosed before the recruitment start date for that cohort. The start date for recruitment is calculated as the earliest date after which at least six patients have been diagnosed with a CCM within the subsequent year.

### *Primary objectives*

1. Descriptive analysis of time-to-event outcomes:

   *First event*

   (i) First ICH in untreated follow-up for those presenting incidentally or with a seizure
   (ii) First ICH/FND in untreated follow-up for those presenting incidentally or with a seizure

   *Recurrent event*

   (iii) First ICH in untreated follow-up for those who either presented with an ICH or FND initially, or second ICH in untreated follow-up for those who presented with a seizure or incidentally and have had a first ICH in follow-up

   (iv) First ICH/FND in untreated follow-up for those who either presented with an ICH or FND initially, or second ICH/FND for those who presented with a seizure or incidentally and have had a first ICH or FND in follow-up.

2. Identification of risk factors for ICH or ICH/FND:

   (i) *a priori* specified predictors of interest

- *core predictors:*
  - prior ICH/FND versus other by individual patient
  - CCM location (brainstem versus other)

- *potential predictors:*
  - sex (female versus male)
  - multiple versus solitary CCM (if sufficient power)
  - age (if sufficient power)

(ii) exploratory predictors

- CCM size
- associated developmental venous anomaly

3. Building and evaluating a multivariable prognostic model:

(i) to model the risk of a future ICH (or a composite endpoint of ICH or FND, if data are available) for an adult with untreated CCM(s) during follow-up

(ii) pre-specified covariates as candidates for inclusion in the model were chosen for clinical significance and comprise the core, potential and exploratory predictors as described above.

### *Secondary objective*

Preliminary analyses, of an exploratory nature only since the current study may not be adequately powered, will be undertaken in order to determine the potential for future work:

a. potential interactions will be investigated in an exploratory manner:

   i. prior ICH/FND and CCM location
   ii. prior ICH/FND and sex
   iii. age and sex.

b. effect of antithrombotic therapy

*Primary outcome events*

(i) Symptomatic ICH

(ii) A composite endpoint of symptomatic ICH or FND.

The composite outcome is important, because both ICH and FND have a similar level of morbidity for the patient, and in certain circumstances an outcome labelled FND may, in reality, be an ICH, but not categorised as such, either because the appropriate neuro-imaging was not performed or because the imaging failed to detect any blood (Al-Shahi Salman et al., 2008). If appropriate, we may perform a subsidiary analysis of the outcomes 'recurrent ICH' or 'recurrent ICH/FND', which may require adjustment of age, CCM location and mode of clinical presentation to be compatible with this first outcome event in follow-up.

*Definitions*

- **Mode of clinical presentation**: In this study when an adult presents with several symptoms, the dominant one is taken as the mode of presentation. For example, a patient may present with a headache, seizure and ICH, but mode of presentation would be recorded as ICH because the headache and seizure are symptomatic of the ICH.

- **Intracranial haemorrhage:** ICH is defined as 'acute or subacute onset symptoms (any of headache, epileptic seizure, impaired consciousness, new/worsened FND referable to the anatomic location of the CCM) and radiological, pathological, surgical or rarely only cerebrospinal fluid evidence of recent extra- and/or intralesional haemorrhage. The mere existence of a haemosiderin halo, or solely an increase in CCM diameter without other evidence of recent haemorrhage, are not considered to constitute haemo-rrhage.' (Al-Shahi Salman et al., 2008)

- **Non-haemorrhagic focal neurological deficit:** A new or worsened FND referable to the CCM anatomic location, which may present with other clinical features of ICH, but without evidence of recent blood on timely brain imaging

and/or pathological examination, or examination of the cerebrospinal fluid (Al-Shahi Salman et al., 2008).

- **Focal neurological deficit not otherwise specified:** This is identical to a non-haemorrhagic FND, with the exception that neither pathological examination, nor cerebrospinal fluid examination, nor timely imaging have been performed at all or at the correct time to establish whether haemorrhage, oedema or lesion growth underlie the clinical deterioration (Al-Shahi Salman et al., 2008).

- **Seizure:** A participant is classified as presenting with an epileptic seizure if the seizure was not symptomatic of a concomitant acute ICH or FND, and there was no more likely cause for the seizure than the CCM.

- **Incidental:** A participant was classified as presenting incidentally if the adult had been asymptomatic, or if the symptoms could not be related to the underlying CCM.

- **Directly or possibly attributable to the CCM:** In some included studies we can examine clinical events (ICH or FND) that are either directly attributable or possibly attributable to the CCM. In the latter instance, although the symptoms are anatomically consistent with the lesion location, it is possible that they may be due to another cause, and neuro-imaging has not been able to provide a definitive explanation of the cause of symptoms.

- **Inception:** This is taken to be the date of first-ever diagnosis of a CCM.

- **Period at risk:** All available follow-up from inception until the outcome event or censoring.

- **Censoring** will take place at the earliest occurrence of any of the following:

    - first interventional treatment (surgical excision or stereotactic radio-surgery)
    - death,

- last available follow-up, or
- truncation of follow-up 5 years after presentation (or median duration of follow-up from all studies)

unless an outcome event occurs sooner.

### *Handling missing data*

During the process of cleaning each dataset, problems of missing data will be addressed by contacting the clinician responsible for providing the data and where possible will be resolved. In cases where this is not possible, missing values will be imputed, if appropriate, using a multiple imputation technique.

### *Completeness of follow-up*

We will use one method of reporting completeness of follow-up (Clark et al., 2002), which calculates the total actual follow-up accrued as a percentage of the total follow-up that was potentially available, before death or the end of the five-year period for the analyses.

### *Heterogeneity*

Heterogeneity is an important consideration, both from the clinical and statistical perspectives, and in this study there are three potential sources of heterogeneity.

#### *(i) Study design*

An example of heterogeneity of study design is that patients in a population-based study may be more likely to present incidentally than patients in a hospital-based study; to account for this source of heterogeneity, the total dataset will be stratified by study design – i.e. population-based cohort vs hospital-based cohort. In addition, length of follow-up is an important consideration as outcome events may require several years of follow-up.

*(ii) Baseline characteristics*

Of particular concern are patient age, sex, mode of clinical presentation, CCM location and multiplicity, as these may influence outcome: for example, patients in a tertiary referral neurosurgery unit may be more likely to harbour brainstem lesions, and patients in an institute specialising in genetics may be more likely to have the familial form of the disease, with multiple lesions, than patients in general hospitals or the community.

*(iii) Hazard ratios*

The final type of heterogeneity is that of hazard ratios (see section 'Identifying and quantifying heterogeneity in hazard ratios' below); this might make pooling (and the derivation of an overall prognostic model) questionable (Borenstein et al., 2009, Ioannidis et al., 2008).

### *Baseline characteristics*

A table of baseline characteristics, stratified by mode of initial clinical presentation, will be presented for each cohort, together with a similar table for the combined cohorts.

- Age at start of follow-up (either CCM diagnosis or other inception point)[5]
- Sex
- CCM multiplicity: single or multiple
- 'Primary' CCM location:*
    - symptomatic CCM; or
    - if asymptomatic and multiple, including a brainstem CCM, then location = brainstem.

  Location will be categorised:

[5] These variables may vary, according to whether analyses are time to first/second event (for adults who present with a seizure or incidentally, and then have an outcome event during follow-up)

        - Cerebellum
        - Deep (basal ganglia, thalamus or choroid)
        - Brainstem (pons, medulla or midbrain)
        - Lobar (all  other)
- Mode of clinical presentation:*
        - incidental
            - if patient was asymptomatic
            - if symptoms could not be attributed – definitely or possibly – to the underlying CCM
        - epileptic seizure
        - ICH(Al-Shahi Salman et al., 2008)
        - FND(Al-Shahi Salman et al., 2008)

## Outcome analyses

In the main 'two step' analysis we will fit univariate and multivariable models to each cohort, using forest plots to display the unadjusted and adjusted estimated hazard ratios, and we will pool these estimates, where appropriate. As a sensitivity analysis, in a 'one step' analysis we will fit models to the entire dataset of all patients pooled from the individual cohorts, with analyses stratified by a study covariate.

### *Individual cohorts*

#### *Descriptive analysis*

We will present tables of the baseline characteristics for each cohort, stratified by mode of clinical presentation, so that the similarity of each cohort at inception can be assessed.

#### *Time-to-event analyses*

We will use Kaplan-Meier survival curves (one minus survival plot) to display the cumulative proportion of the cohort that experiences the ICH primary outcome event; in cohorts where FNDs are recorded, we will separately present Kaplan-Meier survival

curves for the incidence of the other primary outcome event (ICH/FND). Each Kaplan-Meier plot will be stratified by a particular covariate:

- mode of clinical presentation (ICH or FND *vs* other)
- brainstem *vs* other CCM location
- sex (female *vs* male)
- multiple *vs* solitary CCM.

We will use the log-rank test to compare the survival plots for each of these stratifications. The length of follow-up period displayed graphically will be up to five years, but it will be determined by the numbers at risk at specific time points.

*Univariate analyses*

In both the univariate and multivariable analyses of time to one or other primary outcome, we will use the Cox proportional-hazards regression model, provided that the proportional-hazards assumption is fulfilled. The following covariates will be entered in univariate analyses to determine the unadjusted hazard ratio (and 95% confidence interval) for each putative predictor.

*Putative risk factors*

- Covariates of *a priori* interest
    - Core covariates
        - **Mode of clinical presentation** - for survival analyses, mode of clinical presentation will be dichotomised:

          ICH or FND at presentation ($x = 1$) *vs* incidental or seizure at presentation ($x = 0$)

        - **Location** - for survival analyses location will be dichotomised:

          brainstem location ($x = 1$) *vs* other location ($x = 0$)

    - Other covariates of *a priori* interest
        - Age at start of follow-up (as a continuous variable)
        - CCM multiplicity: multiple ($x = 1$) *vs* single ($x = 0$)

- Sex: female ($x = 1$) *vs* male ($x = 0$)

- Other potential covariates, depending on whether they have been recorded
  - CCM size
  - antithrombotic therapy: never ($x = 0$) *vs* ever ($x = 1$)

- Design covariate – for multivariable analyses only
  - cohort

If antithrombotic therapy is included as a potential covariate, then it may need to be modelled as a time-varying covariate.

*Multivariable analyses*

The hazard ratios and 95% confidence intervals will be examined for each covariate in the univariate analyses. In the multivariable analyses, since there is inconsistency about the role of sex as a putative risk factor for ICH or FND, we will force all the covariates of *a priori* interest apart from sex into the model, regardless of their statistical significance in the univariate analyses, because they are of clinical significance; then, adjusting for these four covariates, sex will be included in the model, to ascertain its impact on the outcome.

The following interactions will also be explored in terms of their potential for future research:

- prior ICH/FND and CCM location
- prior ICH/FND and sex
- age and sex

*Sensitivity analysis*

The data from the five cohorts will be pooled and the descriptive analysis, time-to-event analyses, univariate and multivariable analyses described above will be repeated on the entire dataset, stratified by the covariate 'study'.

### *Forest plots*

Estimates of the unadjusted and adjusted hazard ratios for the five *a priori* risk factors for

i. ICH
ii. ICH or FND

will be presented in forest plots, together with the 95% confidence interval for each covariate. The hazard ratios will be adjusted for factors imbalanced at baseline and/or known or suspected to influence CCM prognosis. If appropriate, we will pool all studies and calculate unadjusted and adjusted pooled estimates of the hazard ratios.

### *Identifying and quantifying heterogeneity in hazard ratios*

To identify any heterogeneity between the cohorts in the hazard ratios, we will

- compute $Q$ – the weighted sum of squares of deviation of each effect size from the mean, on a standardized scale;
- estimate $\tau^2$ – variance of the true effect sizes (estimated by $T^2$);
- compute $I^2$ statistic – proportion of observed dispersion that is real, rather than spurious (a measure of inconsistency across the findings of the studies which reflects the extent of overlap of confidence intervals).

## Prognostic model

If heterogeneity between the cohorts is sufficiently modest to enable a prognostic model to be built, patient data in all cohorts will be pooled to form a single dataset. Assuming the proportional-hazards assumption is not violated, the Cox proportional-hazards regression model will be used to model the risk of a future ICH (and FND, if the data are available) for an adult with CCM during untreated follow-up (Harrell et al., 1996, Machin et al., 2006). Pre-specified covariates in the model will be selected for their clinical significance and will be chosen in order from the five covariates of *a priori* interest listed above, namely, prior ICH/FND, brainstem location, age (as a continuous variable), lesion multiplicity, and sex. Other potential covariates include

lesion size, and whether the adult has received antithrombotic therapy. If heterogeneity between the cohorts is substantial, but the proportional-hazards assumption is not violated, then the Cox proportional-hazards regression will be stratified by a 'study' covariate, with covariates of *a priori* interest included in the model (Hosmer et al., 2008, Steyerberg, 2009, Fibrinogen, 2009).

If appropriate, we will round the regression coefficients, estimate the baseline event risk, and then develop a prognostic index by calculating a prognostic score for each adult in the dataset. A frequency distribution of the individual scores will be examined, and two cut-off points at arithmetically convenient points (e.g. 25% with worst prognosis, and 25% with best prognosis) will be used to separate the dataset into high-, medium- and low-risk categories (Machin et al., 2006, Leonard et al., 1991). A Kaplan-Meier plot, stratified by these three risk categories, will then be calculated to illustrate the degree of discrimination achieved by the index.

If the proportional-hazards assumption is seriously violated, then a multivariable logistic regression model will be used, with occurrence of ICH (or FND, if data are available) within the first five years of follow-up as the dependent variable.

### *Model validation*

#### *Internal validation*

It will probably not be possible to validate this model by splitting our current dataset in half, as we will have insufficient outcome events in each portion. However, if it is not possible to use one or more cohorts in developing the model, then these could possibly be used to validate it.

If the model is built using data from all the cohorts, then the internal–external cross-evaluation technique will be used to validate the model internally and adjust the model for overfitting using a shrinkage factor (Debray et al., 2012, Royston et al., 2004). Using this method, the model will be fitted on four of the five cohorts and validated on the fifth, for five occurrences (so that each model is omitted from the validation process in turn) (Royston et al., 2004, May et al., 2004). We will examine the

predictive performance of the model by assessing its calibration and discrimination. Calibration compares the level of agreement between, for example, the model estimation of the probability of an adult experiencing an ICH within five years and the observed frequency of ICH (Moons et al., 2012b). Discrimination describes how well the model splits into those who have the outcome of interest and those who do not. Harrell's concordance index (c-index) will be used to quantify the discriminative ability of the model and calibration will be assessed using plots and the modified Hosmer and Lemeshow test for survival analysis (May and Hosmer, 1998).

## Exploratory analyses

We will explore the potential for future research, depending on the data provided by the different studies.

- Whether an interaction exists between each of the following pairs of covariates:
    - prior ICH / FND and CCM location
    - prior ICH /FND and sex
    - age and sex

- Effect of antithrombotic therapy on adults with untreated CCM.

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# Appendix F: Tables for Chapter 8

**Table A. 1 Estimated risk of intracranial haemorrhage in five-year follow-up, by sex**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | Female | 80 | 5 | 7.3% | 1.1 to 13.5 | 0.032 |
| | Male | 55 | 2 | 4.2% | 0 to 10.0 | 0.029 |
| **Scotland, 2006–2010** | Female | 77 | 2 | 3.6% | 0 to 8.6 | 0.025 |
| | Male | 83 | 5 | 7.1% | 1.0 to 13.2 | 0.031 |
| **Hôpital Lariboisière, Paris** | Female | 47 | 3 | 12.5% | 0 to 26.0 | 0.069 |
| | Male | 34 | 1 | 2.9% | 0 to 8.6 | 0.029 |
| **Mayo Clinic, Rochester, MN** | Female | 143 | 7 | 6.1% | 1.7 to 10.6 | 0.023 |
| | Male | 124 | 13 | 14.2% | 7.0 to 21.5 | 0.037 |
| **Toronto Western Hospital** | Female | 194 | 14 | 9.5% | 4.6 to 14.4 | 0.025 |
| | Male | 151 | 10 | 8.2% | 3.1 to 13.4 | 0.026 |
| **Pooled cohorts** | Female | 541 | 31 | 7.5% | 4.9 to 10.1 | 0.013 |
| | Male | 447 | 31 | 8.8% | 5.8 to 11.8 | 0.015 |

**Table A. 2 Estimated risk of intracranial haemorrhage, by CCM multiplicity**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Mayo Clinic** | Multiple | 49 | 8 | 20.5% | 7.7 to 33.3 | 0.065 |
| | Solitary | 218 | 12 | 7.5% | 3.4 to 11.6 | 0.021 |
| **Toronto** | Multiple | 79 | 2 | 2.6% | 0 to 6.3 | 0.018 |
| | Solitary | 266 | 22 | 11.1% | 6.5 to 15.6 | 0.023 |
| **Paris** | Multiple | 27 | 4 | 21.3% | 2.0 to 40.6 | 0.098 |
| | Solitary | 54 | 0 | – | – | – |
| **Scotland, 1999–2003** | Multiple | 24 | 2 | 9.1% | 0 to 21.2 | 0.062 |
| | Solitary | 111 | 5 | 5.4% | 0.8 to 10.0 | 0.024 |
| **Scotland, 2006–2010** | Multiple | 29 | 2 | 10.6% | 0 to 24.8 | 0.073 |
| | Solitary | 131 | 5 | 4.4% | 0.6 to 8.3 | 0.020 |
| **Pooled cohorts** | Multiple | 208 | 18 | 10.5% | 5.8 to 15.1 | 0.024 |
| | Solitary | 780 | 44 | 7.4% | 5.3 to 9.6 | 0.011 |

**Table A. 3 Estimated risk of intracranial haemorrhage, by age-group**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Mayo Clinic** | ≤ 35 years | 83 | 7 | 11.4% | 3.4 to 19.5 | 0.0411 |
| | 36-53 years | 87 | 5 | 7.5% | 1.1 to 13.9 | 0.0326 |
| | ≥ 54 years | 97 | 8 | 10.6% | 3.5 to 17.7 | 0.0361 |
| **Toronto** | ≤ 35 years | 116 | 12 | 12.3% | 5.6 to 19.1 | 0.0345 |
| | 36-43 years | 141 | 9 | 10.6% | 3.7 to 17.6 | 0.0356 |
| | ≥ 54 years | 88 | 3 | 3.5% | 0 to 7.5 | 0.0200 |
| **Paris** | ≤ 35 years | 29 | 3 | 15.2% | 0 to 31.5 | 0.0834 |
| | 36-53 years | 24 | 1 | 12.5% | 0 to 35.4 | 0.1170 |
| | ≥ 54 years | 28 | 0 | — | — | — |
| **Scotland, 1999–2003** | ≤ 35 years | 50 | 4 | 10.0% | 0.6 to 19.4 | 0.0475 |
| | 36-53 years | 54 | 3 | 6.1% | 0 to 12.8 | 0.0342 |
| | ≥ 54 years | 31 | 0 | — | — | — |
| **Scotland, 2006–2010** | ≤ 35 years | 44 | 1 | 2.8% | 0 to 8.2 | 0.0274 |
| | 36-53 years | 52 | 4 | 8.4% | 0.5 to 16.4 | 0.0405 |
| | ≥ 54 years | 64 | 2 | 4.8% | 0 to 11.2 | 0.0329 |
| **Pooled cohorts** | ≤ 35 years | 322 | 27 | 10.6% | 6.7 to 14.5 | 0.0197 |
| | 36-53 years | 358 | 22 | 8.2% | 4.8 to 11.5 | 0.0170 |
| | ≥ 54 years | 308 | 13 | 5.5% | 2.5 to 8.5 | 0.0152 |

**Table A. 4 Estimated risk of clinical event, by mode of presentation: ICH or FND vs other presentation**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | ICH/FND presentation | 38 | 12 | 37.6% | 20.5 to 54.7 | 0.087 |
| | Other presentation | 97 | 8 | 9.4% | 3.2 to 15.6 | 0.032 |
| **Scotland, 2006–2010** | ICH/FND presentation | 41 | 10 | 30.8% | 14.5 to 47.2 | 0.084 |
| | Other presentation | 119 | 3 | 2.7% | 0 to 5.6 | 0.015 |
| **Toronto** | ICH/FND presentation | 175 | 50 | 35.6% | 27.2 to 43.9 | 0.042 |
| | Other presentation | 170 | 5 | 4.5% | 0.4 to 8.6 | 0.021 |
| **Pooled cohorts** | ICH/FND presentation | 254 | 72 | 35.3% | 28.4 to 42.1 | 0.035 |
| | Other presentation | 386 | 16 | 5.2% | 2.6 to 7.8 | 0.013 |

**Table A. 5 Estimated risk of clinical event, by CCM location**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | Brainstem | 17 | 8 | 47.1% | 23.3 to 70.8 | 0.121 |
| | Other location | 118 | 12 | 12.1% | 5.7 to 18.6 | 0.033 |
| **Scotland, 2006–2010** | Brainstem | 25 | 10 | 50.3% | 26.7 to 73.9 | 0.121 |
| | Other location | 135 | 3 | 2.4% | 0 to 5.1 | 0.014 |
| **Toronto** | Brainstem | 102 | 35 | 43.4% | 31.7 to 55.0 | 0.059 |
| | Other location | 243 | 20 | 10.7% | 6.1 to 15.4 | 0.024 |
| **Pooled cohorts** | Brainstem | 144 | 53 | 44.5% | 35.0 to 54.0 | 0.048 |
| | Other location | 496 | 35 | 8.8% | 6.0 to 11.7 | 0.015 |

**Table A. 6 Estimated risk of clinical event, by sex**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | Female | 80 | 16 | 22.8% | 12.9 to 32.7 | 0.050 |
| | Male | 55 | 4 | 8.5% | 0.5 to 16.4 | 0.041 |
| **Scotland, 2006–2010** | Female | 77 | 6 | 9.8% | 2.2 to 17.3 | 0.039 |
| | Male | 83 | 7 | 9.6% | 2.7 to 16.4 | 0.035 |
| **Toronto** | Female | 194 | 29 | 19.2% | 12.7 to 25.7 | 0.033 |
| | Male | 151 | 26 | 21.9% | 14.1 to 29.8 | 0.040 |
| **Pooled cohorts** | Female | 351 | 51 | 18.0% | 13.4 to 22.6 | 0.023 |
| | Male | 289 | 37 | 15.8% | 10.9 to 20.6 | 0.025 |

**Table A. 7 Estimated risk of clinical event, by CCM multiplicity**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | Multiple | 24 | 5 | 23.8% | 5.3 to 42.2 | 0.094 |
| | Solitary | 111 | 15 | 15.7% | 8.4 to 23.0 | 0.037 |
| **Scotland, 2006–2010** | Multiple | 29 | 2 | 10.6% | 0 to 24.8 | 0.073 |
| | Solitary | 131 | 11 | 9.5% | 4.1 to 14.9 | 0.028 |
| **Toronto** | Multiple | 79 | 11 | 17.5% | 7.7 to 27.2 | 0.050 |
| | Solitary | 266 | 44 | 21.5% | 15.6 to 27.5 | 0.030 |
| **Pooled cohorts** | Multiple | 132 | 18 | 17.0% | 9.6 to 24.4 | 0.038 |
| | Solitary | 508 | 70 | 17.0% | 13.2 to 20.7 | 0.019 |

**Table A. 8 Estimated risk of clinical event, by age-group**

| Study | Risk factor | Number of adults | Events | 5-year estimated risk | 95% confidence interval | SE |
|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | ≤ 35 years | 50 | 9 | 21.6% | 9.0 to 34.1 | 0.0641 |
| | 36-53 years | 54 | 7 | 14.2% | 4.4 to 23.9 | 0.0497 |
| | ≥ 54 years | 31 | 4 | 15.1% | 1.3 to 28.9 | 0.0704 |
| **Scotland, 2006–2010** | ≤ 35 years | 44 | 2 | 5.2% | 0 to 12.2 | 0.0359 |
| | 36-53 years | 52 | 6 | 12.4% | 3.1 to 21.7 | 0.0474 |
| | ≥ 54 years | 64 | 5 | 10.4% | 1.6 to 19.2 | 0.0447 |
| **Toronto** | ≤ 35 years | 116 | 19 | 19.2% | 11.2 to 27.1 | 0.0405 |
| | 36-43 years | 141 | 28 | 28.7% | 19.0 to 38.4 | 0.0496 |
| | ≥ 54 years | 88 | 8 | 11.6% | 3.6 to 19.6 | 0.0407 |
| **Pooled cohorts** | ≤ 35 years | 210 | 30 | 17.3% | 11.5 to 23.0 | 0.0293 |
| | 36-53 years | 247 | 41 | 20.8% | 14.9 to 26.6 | 0.0298 |
| | ≥ 54 years | 183 | 17 | 11.7% | 6.3 to 17.2 | 0.0278 |

**Table A. 9 Analysis of time to first intracranial haemorrhage, stratified by sex**

| Study | Sex | Number | Events (*n*) | Log rank | *p* | Hazard ratio[a] | 95% CI | *p* | Adjusted hazard ratio[b] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mayo Clinic** | female | 143 | 7 | 3.43 | 0.064 | 0.43 | 0.2 to 1.1 | 0.072 | 0.40 | 0.2 to 1.0 | 0.050 |
| | male | 124 | 13 | | | | | | | | |
| **Toronto** | female | 194 | 14 | 0.08 | 0.776 | 1.13 | 0.5 to 2.5 | 0.776 | 0.99 | 0.4 to 2.2 | 0.972 |
| | male | 151 | 10 | | | | | | | | |
| **Paris** | female | 47 | 3 | 0.387 | 0.534 | 2.02 | 0.2 to 19.5 | 0.542 | 0.83 | 0.1 to 12.8 | 0.896 |
| | male | 34 | 1 | | | | | | | | |
| **Scotland, 1999–2003** | female | 80 | 5 | 0.41 | 0.520 | 1.70 | 0.3 to 8.8 | 0.525 | 0.89 | 0.2 to 5.4 | 0.900 |
| | male | 55 | 2 | | | | | | | | |
| **Scotland, 2006–2010** | female | 77 | 2 | 1.17 | 0.280 | 0.42 | 0.1 to 2.1 | 0.295 | 0.45 | 0.1 to 2.4 | 0.349 |
| | male | 83 | 5 | | | | | | | | |
| **Pooled cohorts, unstratified** | female | 541 | 31 | 0.696 | 0.404 | 0.81 | 0.5 to 1.3 | 0.405 | 0.69 | 0.4 to 1.1 | 0.148 |
| | male | 447 | 31 | | | | | | | | |
| **Pooled cohorts, stratified by study** | female | 541 | 31 | 0.759 | 0.384 | 0.80 | 0.5 to 1.3 | 0.385 | 0.69 | 0.4 to 1.1 | 0.150 |
| | male | 447 | 31 | | | | | | | | |

[a] Hazard ratio from univariate analysis. [b] Hazard ratio is adjusted for presentation and CCM location.

**Table A. 10 Analysis of time to first intracranial haemorrhage, stratified by CCM multiplicity**

| Study | Values | Number | Events (*n*) | Log rank | *p* | Hazard ratio[a] | 95% CI | *p* | Adjusted hazard ratio[b] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mayo Clinic** | multiple CCM | 49 | 8 | 7.18 | 0.007 | 3.18 | 1.3 to 7.8 | 0.011 | 3.07 | 1.2 to 7.6 | 0.015 |
| | solitary CCM | 218 | 12 | | | | | | | | |
| **Toronto** | multiple CCM | 79 | 2 | 3.43 | 0.064 | 0.28 | 0.1 to 1.2 | 0.083 | 0.24 | 0.1 to 1.03 | 0.055 |
| | solitary CCM | 266 | 22 | | | | | | | | |
| **Paris** | multiple CCM | 27 | 4 | – | – | – | – | – | – | – | – |
| | solitary CCM | 54 | 0 | | | | | | | | |
| **Scotland, 1999–2003** | multiple CCM | 24 | 2 | 0.64 | 0.425 | 1.93 | 0.4 to 9.9 | 0.433 | 2.38 | 0.5 to 12.7 | 0.310 |
| | solitary CCM | 111 | 5 | | | | | | | | |
| **Scotland, 2006–2010** | multiple CCM | 29 | 2 | 0.74 | 0.390 | 2.03 | 0.4 to 10.5 | 0.400 | 1.08 | 0.2 to 5.8 | 0.928 |
| | solitary CCM | 131 | 5 | | | | | | | | |
| **Pooled cohorts, unstratified** | multiple CCM | 208 | 18 | 2.32 | 0.128 | 1.53 | 0.9 to 2.6 | 0.131 | 1.36 | 0.8 to 2.4 | 0.267 |
| | solitary CCM | 780 | 44 | | | | | | | | |
| **Pooled cohorts, stratified by study** | multiple CCM | 208 | 18 | 2.18 | 0.140 | 1.52 | 0.9 to 2.6 | 0.142 | 1.42 | 0.8 to 2.5 | 0.219 |
| | solitary CCM | 780 | 44 | | | | | | | | |

[a] Hazard ratio from univariate analysis. [b] Hazard ratio is adjusted for presentation and CCM location.

**Table A. 11 Analysis of time to first intracranial haemorrhage, stratified by age (3 groups)**

| Study | Values | Number | Events (*n*) | Log rank[a] | *p* | Hazard ratio[b] | 95% CI | *p* | Adjusted hazard ratio[c] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mayo Clinic** | ≤ 35 years | 83 | 7 | | | 1.13 | 0.4 to 3.1 | 0.810 | 1.08 | 0.4 to 3.0 | 0.882 |
| | 36-53 years | 87 | 5 | 0.04 | 0.836 | 0.78 | 0.3 to 2.4 | 0.655 | 0.60 | 0.2 to 1.9 | 0.375 |
| | ≥ 54 years | 97 | 8 | | | 1.00 | – | | 1.00 | – | |
| **Toronto** | ≤ 35 years | 116 | 12 | | | 3.16 | 0.9 to 11.2 | 0.074 | 3.29 | 0.9 to 11.7 | 0.065 |
| | 36-53 years | 141 | 9 | 3.60 | 0.058 | 2.13 | 0.6 to 7.9 | 0.256 | 2.44 | 0.7 to 9.1 | 0.182 |
| | ≥ 54 years | 88 | 3 | | | 1.00 | – | | 1.00 | – | |
| **Paris** | ≤ 35 years | 29 | 3 | | | – | – | | – | – | |
| | 36-53 years | 24 | 1 | 3.04 | 0.081 | – | – | | – | – | |
| | ≥ 54 years | 28 | 0 | | | – | – | | – | – | |
| **Scotland, 1999–2003** | ≤ 35 years | 50 | 4 | | | – | – | | – | – | |
| | 36-53 years | 54 | 3 | 2.48 | 0.115 | – | – | | – | – | |
| | ≥ 54 years | 31 | 0 | | | – | – | | – | – | |
| **Scotland, 2006–2010** | ≤ 35 years | 44 | 1 | | | 0.77 | 0.1 to 8.5 | 0.831 | 4.64 | 0.3 to 62.3 | 0.246 |
| | 36-53 years | 52 | 4 | 0.00 | 0.993 | 2.63 | 0.5 to 14.3 | 0.265 | 20.13 | 2.2 to 182.7 | 0.008 |
| | ≥ 54 years | 64 | 2 | | | 1.00 | – | | 1.00 | – | |

[a] log rank test for trend, 1 degree of freedom. [b] Hazard ratio from univariate analysis. [c] Hazard ratio is adjusted for presentation and CCM location.

**Table A. 11 *contd***

| Study | Values | Number | Events (*n*) | Log rank[a] | *p* | Hazard ratio[b] | 95% CI | *p* | Adjusted hazard ratio[c] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pooled cohorts, unstratified** | ≤ 35 years | 322 | 27 | 5.05 | 0.025 | 2.10 | 1.1 to 4.1 | 0.028 | 2.26 | 1.2 to 4.4 | 0.016 |
| | 36-53 years | 358 | 22 | | | 1.56 | 0.8 to 3.1 | 0.203 | 1.59 | 0.8 to 3.2 | 0.184 |
| | ≥ 54 years | 308 | 13 | | | 1.00 | – | | 1.00 | – | |
| **Pooled cohorts, stratified by study** | ≤ 35 years | 322 | 27 | 5.01 | 0.025 | 2.11 | 1.1 to 4.1 | 0.028 | 2.34 | 1.2 to 4.6 | 0.013 |
| | 36-53 years | 358 | 22 | | | 1.58 | 0.8 to 3.1 | 0.196 | 1.61 | 0.8 to 3.2 | 0.177 |
| | ≥ 54 years | 308 | 13 | | | 1.00 | – | | 1.00 | – | |

[a] log rank test for trend, 1 degree of freedom. [b] Hazard ratio from univariate analysis. [c] Hazard ratio is adjusted for presentation and CCM location.

**Table A. 12 Analysis of time to first intracranial haemorrhage, stratified by age (4 groups)**

| Study | Values | Number | Events (*n*) | Log rank[a] | *p* | Hazard ratio[b] | 95% CI | *p* | Adjusted hazard ratio[c] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mayo Clinic** | ≤ 30 years | 62 | 5 | 0.12 | 0.727 | 0.91 | 0.3 to 2.9 | 0.874 | 0.94 | 0.3 to 3.0 | 0.921 |
| | 31-45 years | 64 | 3 | | | 0.51 | 0.1 to 2.0 | 0.330 | 0.46 | 0.1 to 1.8 | 0.257 |
| | 46-60 years | 71 | 5 | | | 0.70 | 0.2 to 2.2 | 0.540 | 0.72 | 0.2 to 2.3 | 0.571 |
| | ≥ 60 years | 70 | 7 | | | 1.00 | | | 1.00 | | |
| **Toronto** | ≤ 30 years | 68 | 6 | 1.75 | 0.186 | 1.36 | 0.3 to 5.4 | 0.663 | 1.39 | 0.3 to 5.6 | 0.642 |
| | 31-45 years | 134 | 13 | | | 1.68 | 0.5 to 5.9 | 0.421 | 1.53 | 0.4 to 5.4 | 0.510 |
| | 46-60 years | 97 | 2 | | | 0.36 | 0.1 to 2.2 | 0.262 | 0.34 | 0.1 to 2.1 | 0.244 |
| | ≥ 60 years | 46 | 3 | | | 1.00 | | | 1.00 | | |
| **Paris** | ≤ 30 years | 23 | 2 | 1.26 | 0.261 | – | – | – | – | – | – |
| | 31-45 years | 21 | 1 | | | – | – | – | – | – | – |
| | 46-60 years | 21 | 1 | | | – | – | – | – | – | – |
| | ≥ 60 years | 16 | 0 | | | – | – | – | – | – | – |
| **Scotland, 1999–2003** | ≤ 30 years | 29 | 1 | 0.32 | 0.570 | – | – | – | – | – | – |
| | 31-45 years | 51 | 4 | | | – | – | – | – | – | – |
| | 46-60 years | 36 | 2 | | | – | – | – | – | – | – |
| | ≥ 60 years | 19 | 0 | | | – | – | – | – | – | – |
| **Scotland, 2006–2010** | ≤ 30 years | 26 | 0 | 0.67 | 0.412 | – | – | – | – | – | – |
| | 31-45 years | 52 | 5 | | | – | – | – | – | – | – |
| | 46-60 years | 43 | 2 | | | – | – | – | – | – | – |
| | ≥ 60 years | 39 | 0 | | | – | – | – | – | – | – |

**Table A. 12 *contd***

| Study | Values | Number | Events (*n*) | Log rank[a] | *p* | Hazard ratio[b] | 95% CI | *p* | Adjusted hazard ratio[c] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pooled cohorts, unstratified** | ≤ 30 years | 208 | 14 | 1.76 | 0.185 | 1.32 | 0.6 to 3.0 | 0.499 | 1.52 | 0.7 to 3.4 | 0.315 |
| | 31-45 years | 322 | 26 | | | 1.64 | 0.8 to 3.4 | 0.182 | 1.56 | 0.8 to 3.2 | 0.234 |
| | 46-60 years | 268 | 12 | | | 0.86 | 0.4 to 2.0 | 0.724 | 0.96 | 0.4 to 2.2 | 0.925 |
| | ≥ 60 years | 190 | 10 | | | 1.00 | | | 1.00 | | |
| **Pooled cohorts, stratified by study** | ≤ 30 years | 208 | 14 | 1.75 | 0.186 | 1.32 | 0.6 to 3.0 | 0.502 | 1.55 | 0.7 to 3.5 | 0.298 |
| | 31-45 years | 322 | 26 | | | 1.71 | 0.8 to 3.6 | 0.158 | 1.65 | 0.8 to 3.5 | 0.183 |
| | 46-60 years | 268 | 12 | | | 0.87 | 0.4 to 2.0 | 0.747 | 0.99 | 0.4 to 2.3 | 0.972 |
| | ≥ 60 years | 190 | 10 | | | 1.00 | | | 1.00 | | |

[a] log rank test for trend, 1 degree of freedom. [b] Hazard ratio from univariate analysis. [c] Hazard ratio is adjusted for presentation and CCM location.

**Table A. 13 Analysis of time to first clinical event, stratified by presentation**

| Study | Values | Number | Events (*n*) | log rank | *p* | Hazard ratio[a] | 95% CI | *p* | Adjusted hazard ratio[b] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | ICH or FND | 38 | 12 | 13.9 | <0.0001 | 4.71 | 1.9 to 11.5 | 0.001 | 3.20 | 1.2 to 8.7 | 0.023 |
| | Incidental or seizure | 97 | 8 | | | | | | | | |
| **Scotland, 2006–2010** | ICH or FND | 41 | 10 | 22.1 | <0.0001 | 11.52 | 3.2 to 41.9 | <0.0001 | 4.90 | 1.2 to 19.4 | 0.024 |
| | Incidental or seizure | 119 | 3 | | | | | | | | |
| **Toronto** | ICH or FND | 175 | 50 | 42.6 | <0.0001 | 11.30 | 4.5 to 28.3 | <0.0001 | 7.59 | 2.9 to 19.8 | <0.0001 |
| | Incidental or seizure | 170 | 5 | | | | | | | | |
| **Pooled cohorts, unstratified** | ICH or FND | 254 | 72 | 82.9 | <0.0001 | 8.24 | 4.8 to 14.2 | <0.0001 | 5.09 | 2.8 to 9.1 | <0.0001 |
| | Incidental or seizure | 386 | 16 | | | | | | | | |
| **Pooled cohorts, stratified by study** | ICH or FND | 254 | 72 | 75.1 | <0.0001 | 8.24 | 4.7 to 14.3 | <0.0001 | 5.20 | 2.9 to 9.4 | <0.0001 |
| | Incidental or seizure | 386 | 16 | | | | | | | | |

[a] Hazard ratio from univariate analysis.

[b] Hazard ratio is adjusted for CCM location.

**Table A. 14 Analysis of time to first clinical event, stratified by CCM location**

| Study | Values | Number | Events (*n*) | log rank | *p* | Hazard ratio[a] | 95% CI | *p* | Adjusted hazard ratio[b] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | Brainstem | 17 | 8 | 16.17 | <0.0001 | 5.18 | 2.1 to 12.7 | <0.0001 | 2.97 | 1.1 to 8.1 | 0.032 |
| | Other location | 118 | 12 | | | | | | | | |
| **Scotland, 2006–2010** | Brainstem | 25 | 10 | 46.47 | <0.0001 | 22.58 | 6.2 to 82.5 | <0.0001 | 12.84 | 3.2 to 51.1 | <0.0001 |
| | Other location | 135 | 3 | | | | | | | | |
| **Toronto** | Brainstem | 102 | 35 | 39.92 | <0.0001 | 4.94 | 2.9 to 8.6 | <0.0001 | 2.58 | 1.5 to 4.6 | 0.001 |
| | Other location | 243 | 20 | | | | | | | | |
| **Pooled cohorts, unstratified** | Brainstem | 144 | 53 | 92.48 | <0.0001 | 6.26 | 4.1 to 9.6 | <0.0001 | 3.20 | 2.0 to 5.1 | <0.0001 |
| | Other location | 496 | 35 | | | | | | | | |
| **Pooled cohorts, stratified by study** | Brainstem | 144 | 53 | 84.76 | <0.0001 | 6.23 | 4.0 to 9.7 | <0.0001 | 3.32 | 2.1 to 5.3 | <0.0001 |
| | Other location | 496 | 35 | | | | | | | | |

[a] Hazard ratio from univariate analysis.

[b] Hazard ratio is adjusted for presentation.

**Table A. 15 Analysis of time to first clinical event, stratified by sex**

| Study | Values | Number | Events (*n*) | log rank | *p* | Hazard ratio[a] | 95% CI | *p* | Adjusted hazard ratio[b] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | female | 80 | 16 | 3.91 | 0.048 | 2.88 | 0.96 to 8.6 | 0.059 | 1.88 | 0.6 to 6.0 | 0.281 |
| | male | 55 | 4 | | | | | | | | |
| **Scotland, 2006–2010** | female | 77 | 6 | 0.04 | 0.844 | 0.90 | 0.3 to 2.7 | 0.844 | 1.02 | 0.3 to 3.1 | 0.974 |
| | male | 83 | 7 | | | | | | | | |
| **Toronto** | female | 194 | 29 | 0.15 | 0.699 | 0.90 | 0.5 to 1.5 | 0.699 | 0.78 | 0.5 to 1.3 | 0.365 |
| | male | 151 | 26 | | | | | | | | |
| **Pooled cohorts, unstratified** | female | 351 | 51 | 0.48 | 0.49 | 1.16 | 0.8 to 1.8 | 0.491 | 0.94 | 0.6 to 1.4 | 0.780 |
| | male | 289 | 37 | | | | | | | | |
| **Pooled cohorts, stratified by study** | female | 351 | 51 | 0.31 | 0.579 | 1.13 | 0.7 to 1.7 | 0.580 | 0.88 | 0.6 to 1.4 | 0.558 |
| | male | 289 | 37 | | | | | | | | |

[a] Hazard ratio from univariate analysis.

[b] Hazard ratio is adjusted for presentation and CCM location.

**Table A. 16 Analysis of time to first clinical event, stratified by CCM multiplicity**

| Study | Values | Number | Events (*n*) | log rank | *p* | Hazard ratio[a] | 95% CI | *p* | Adjusted hazard ratio[b] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | multiple | 24 | 5 | 1.05 | 0.305 | 1.69 | 0.6 to 4.6 | 0.31 | 2.08 | 0.7 to 5.9 | 0.166 |
| | solitary | 111 | 15 | | | | | | | | |
| **Scotland, 2006–2010** | multiple | 29 | 2 | 0.011 | 0.916 | 0.92 | 0.2 to 4.2 | 0.916 | 0.47 | 0.1 to 2.2 | 0.328 |
| | solitary | 131 | 11 | | | | | | | | |
| **Toronto** | multiple | 79 | 11 | 0.70 | 0.402 | 0.76 | 0.4 to 1.5 | 0.404 | 0.65 | 0.3 to 1.3 | 0.207 |
| | solitary | 266 | 44 | | | | | | | | |
| **Pooled cohorts, unstratified** | multiple | 132 | 18 | 0.008 | 0.930 | 0.98 | 0.58 to 1.64 | 0.930 | 0.79 | 0.5 to 1.3 | 0.368 |
| | solitary | 508 | 70 | | | | | | | | |
| **Pooled cohorts, stratified by study** | multiple | 132 | 18 | 0.085 | 0.771 | 0.93 | 0.55 to 1.56 | 0.771 | 0.82 | 0.5 to 1.4 | 0.464 |
| | solitary | 508 | 70 | | | | | | | | |

[a] Hazard ratio from univariate analysis.

[b] Hazard ratio is adjusted for presentation and CCM location.

**Table A. 17 Analysis of time to first clinical event, stratified by age (3 groups)**

| Study | Values | Number | Events (*n*) | Log rank[a] | *p* | Hazard ratio[b] | 95% CI | *p* | Adjusted hazard ratio[c] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Scotland, 1999–2003** | ≤ 35 years | 50 | 9 | | | 1.34 | 0.4 to 4.4 | 0.625 | 2.05 | 0.6 to 6.9 | 0.245 |
| | 36-53 years | 54 | 7 | 0.40 | 0.530 | 0.88 | 0.3 to 3.0 | 0.843 | 1.09 | 0.3 to 3.8 | 0.891 |
| | ≥ 54 years | 31 | 4 | | | 1.00 | | | 1.00 | | |
| **Scotland, 2006–2010** | ≤ 35 years | 44 | 2 | | | 0.61 | 0.1 to 3.1 | 0.551 | 1.90 | 0.3 to 10.4 | 0.462 |
| | 36-53 years | 52 | 6 | 0.16 | 0.694 | 1.59 | 0.5 to 5.2 | 0.445 | 4.98 | 1.3 to 18.6 | 0.017 |
| | ≥ 54 years | 64 | 5 | | | 1.00 | | | 1.00 | | |
| **Toronto** | ≤ 35 years | 116 | 19 | | | 1.87 | 0.8 to 4.3 | 0.138 | 1.96 | 0.9 to 4.5 | 0.109 |
| | 36-53 years | 141 | 28 | 1.40 | 0.237 | 2.59 | 1.2 to 5.7 | 0.018 | 2.99 | 1.4 to 6.6 | 0.007 |
| | ≥ 54 years | 88 | 8 | | | 1.00 | | | 1.00 | | |
| **Pooled cohorts, unstratified** | ≤ 35 years | 210 | 30 | | | 1.58 | 0.9 to 2.9 | 0.130 | 1.84 | 1.0 to 3.3 | 0.046 |
| | 36-53 years | 247 | 41 | 1.81 | 0.178 | 1.94 | 1.1 to 3.4 | 0.022 | 2.43 | 1.4 to 4.3 | 0.002 |
| | ≥ 54 years | 183 | 17 | | | 1.00 | | | 1.00 | | |
| **Pooled cohorts, stratified by study** | ≤ 35 years | 210 | 30 | | | 1.47 | 0.8 to 2.7 | 0.205 | 1.86 | 1.0 to 3.4 | 0.044 |
| | 36-53 years | 247 | 41 | 1.14 | 0.285 | 1.83 | 1.0 to 3.2 | 0.038 | 2.41 | 1.4 to 4.3 | 0.003 |
| | ≥ 54 years | 183 | 17 | | | 1.00 | | | 1.00 | | |

[a] log rank test for trend, 1 degree of freedom. [b] Hazard ratio from univariate analysis. [c] Hazard ratio is adjusted for presentation and CCM location.

**Table A. 18 Analysis of time to first clinical event, stratified by age (4 groups)**

| Study | Values | Number | Events (*n*) | Log rank[a] | *p* | Hazard ratio[b] | 95% CI | *p* | Adjusted hazard ratio[c] | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Toronto** | ≤ 30 years | 68 | 9 | | | 1.23 | 0.4 to 3.7 | 0.711 | 1.28 | 0.4 to 3.8 | 0.657 |
| | 31-45 years | 134 | 30 | 0.90 | 0.343 | 2.37 | 0.9 to 6.1 | 0.074 | 2.21 | 0.9 to 5.7 | .0102 |
| | 46-60 years | 97 | 11 | | | 1.23 | 0.4 to 3.5 | 0.700 | 1.18 | 0.4 to 3.4 | 0.757 |
| | ≥ 60 years | 46 | 5 | | | 1.00 | | | 1.00 | | |
| **Scotland, 1999–2003** | ≤ 30 years | 29 | 6 | | | 0.86 | 0.2 to 3.1 | 0.818 | 1.42 | 0.4 to 5.2 | 0.594 |
| | 31-45 years | 51 | 7 | 0.13 | 0.720 | 0.59 | 0.2 to 2.0 | 0.405 | 0.78 | 0.2 to 2.7 | 0.691 |
| | 46-60 years | 36 | 3 | | | 0.32 | 0.1 to 1.4 | 0.133 | 0.51 | 0.1 to 2.4 | 0.393 |
| | ≥ 60 years | 19 | 4 | | | | | | | | |
| **Scotland, 2006–2010** | ≤ 30 years | 26 | 0 | | | – | – | – | – | – | – |
| | 31-45 years | 52 | 7 | 0.10 | 0.748 | 1.88 | 0.5 to 7.3 | 0.361 | 3.76 | 0.9 to 15.2 | 0.062 |
| | 46-60 years | 43 | 3 | | | 0.81 | 0.2 to 4.0 | 0.798 | 0.94 | 0.2 to 4.7 | 0.944 |
| | ≥ 60 years | 39 | 3 | | | 1.00 | | | 1.00 | | |
| **Pooled cohorts, unstratified** | ≤ 30 years | 123 | 15 | | | 1.02 | 0.5 to 2.2 | 0.959 | 1.22 | 0.6 to 2.6 | 0.613 |
| | 31-45 years | 237 | 44 | 1.12 | 0.290 | 1.73 | 0.9 to 3.3 | 0.091 | 1.77 | 0.9 to 3.4 | 0.078 |
| | 46-60 years | 176 | 17 | | | 0.85 | 0.4 to 1.8 | 0.659 | 0.93 | 0.4 to 1.9 | 0.841 |
| | ≥ 60 years | 104 | 12 | | | 1.00 | | | 1.00 | | |
| **Pooled cohorts, stratified by study** | ≤ 30 years | 123 | 15 | | | 0.93 | 0.4 to 2.0 | 0.861 | 1.22 | 0.6 to 2.6 | 0.617 |
| | 31-45 years | 237 | 44 | 0.62 | 0.433 | 1.59 | 0.8 to 3.0 | 0.156 | 1.76 | 0.9 to 3.4 | 0.088 |
| | 46-60 years | 176 | 17 | | | 0.80 | 0.4 to 1.7 | 0.564 | 0.94 | 0.4 to 2.0 | 0.864 |
| | ≥ 60 years | 104 | 12 | | | 1.00 | | | 1.00 | | |

[a] log rank test for trend, 1 degree of freedom. [b] Hazard ratio from univariate analysis. [c] Hazard ratio is adjusted for presentation and CCM location.

**Table A. 19 Model A: comparison of analyses, unstratified and stratified by 'study'**

| Predictor | *Unstratified* | | | | *Stratified by 'study'* | | | |
|---|---|---|---|---|---|---|---|---|
| | *b* | SE(*b*) | Hazard ratio | | *b* | SE(*b*) | Hazard ratio | |
| | | | Estimate | 95% CI | | | Estimate | 95% CI |
| ***ICH only*** | | | | | | | | |
| **ICH/FND presentation** | 1.580 | 0.351 | 4.854 | 2.438–9.665 | 1.559 | 0.355 | 4.950 | 2.467–9.932 |
| **Brainstem location** | 1.1420 | 0.285 | 3.064 | 1.753–5.357 | 1.124 | 0.288 | 3.077 | 1.751–5.408 |
| ***Clinical event*** | | | | | | | | |
| **ICH/FND presentation** | 1.627 | 0.299 | 5.088 | 2.834–9.134 | 1.648 | 0.303 | 5.195 | 2.867–9.416 |
| **Brainstem location** | 1.162 | 0.235 | 3.196 | 2.014–5.070 | 1.201 | 0.238 | 3.323 | 2.084–5.297 |

**Table A. 20 Model B: comparison of analyses, unstratified and stratified by 'study'**

| Predictor | *Unstratified* | | | | *Stratified by 'study'* | | | |
|---|---|---|---|---|---|---|---|---|
| | *b* | SE(*b*) | Hazard ratio | | *b* | SE(*b*) | Hazard ratio | |
| | | | Estimate | 95% CI | | | Estimate | 95% CI |
| ***ICH only*** | | | | | | | | |
| **1 risk factor** | 1.375 | 0.403 | 3.955 | 1.795–8.716 | 1.397 | 0.405 | 4.042 | 1.826–8.948 |
| **2 risk factors** | 2.659 | 0.358 | 14.283 | 7.086–28.789 | 2.683 | 0.365 | 14.627 | 7.153–29.909 |
| ***Clinical event*** | | | | | | | | |
| **1 risk factor** | 1.809 | 0.354 | 6.105 | 3.050–12.223 | 1.842 | 0.357 | 6.309 | 3.134–12.702 |
| **2 risk factors** | 2.893 | 0.335 | 18.046 | 9.361–34.786 | 2.954 | 0.344 | 19.180 | 9.769–37.657 |

# Appendix G: Figures from Chapter 8

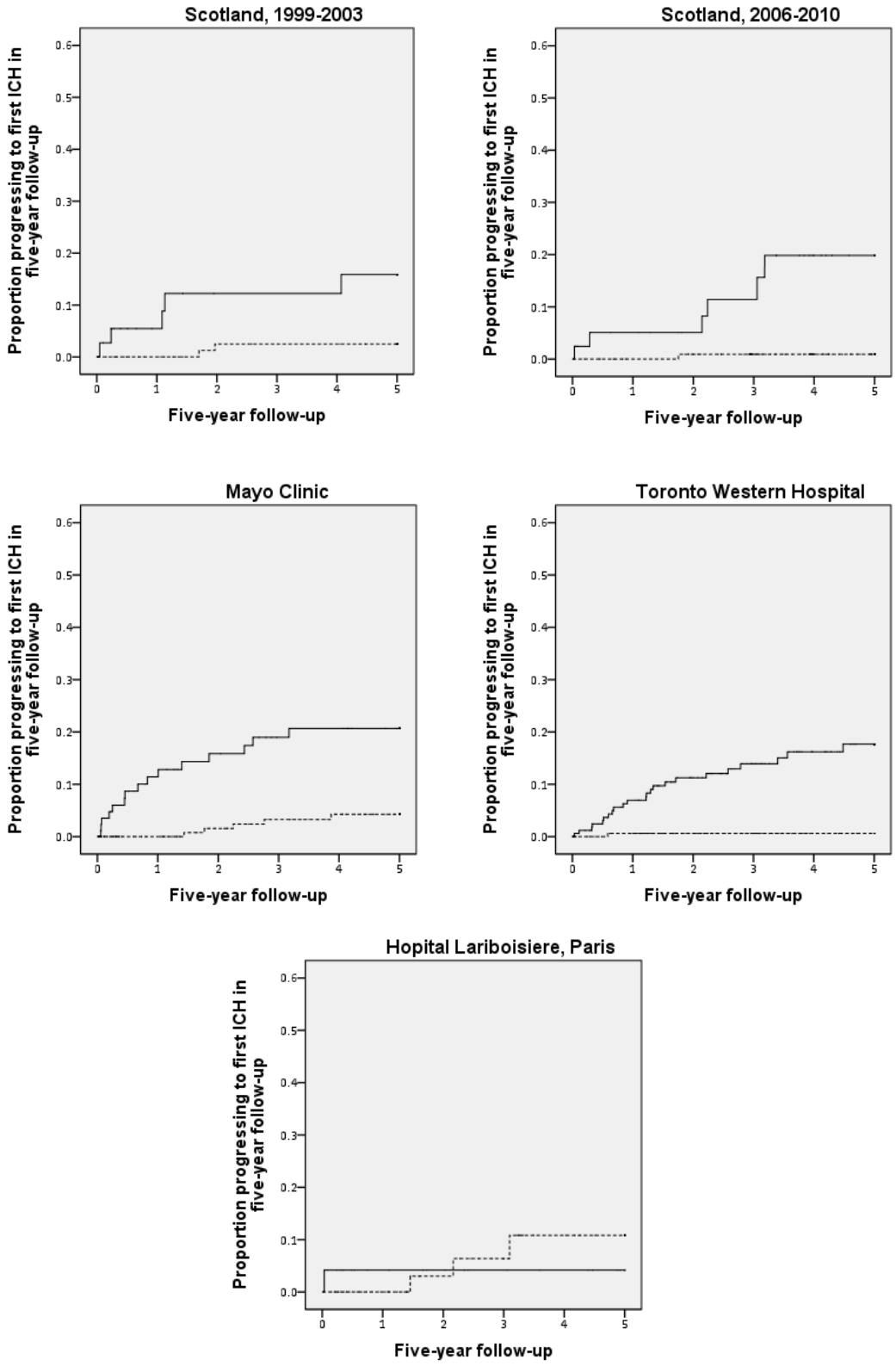



**Figure A. 1 Kaplan-Meier plots comparing estimated risk of first ICH, stratified by presentation: ICH or FND presentation (continuous line) *vs* other presentation (dotted line)**

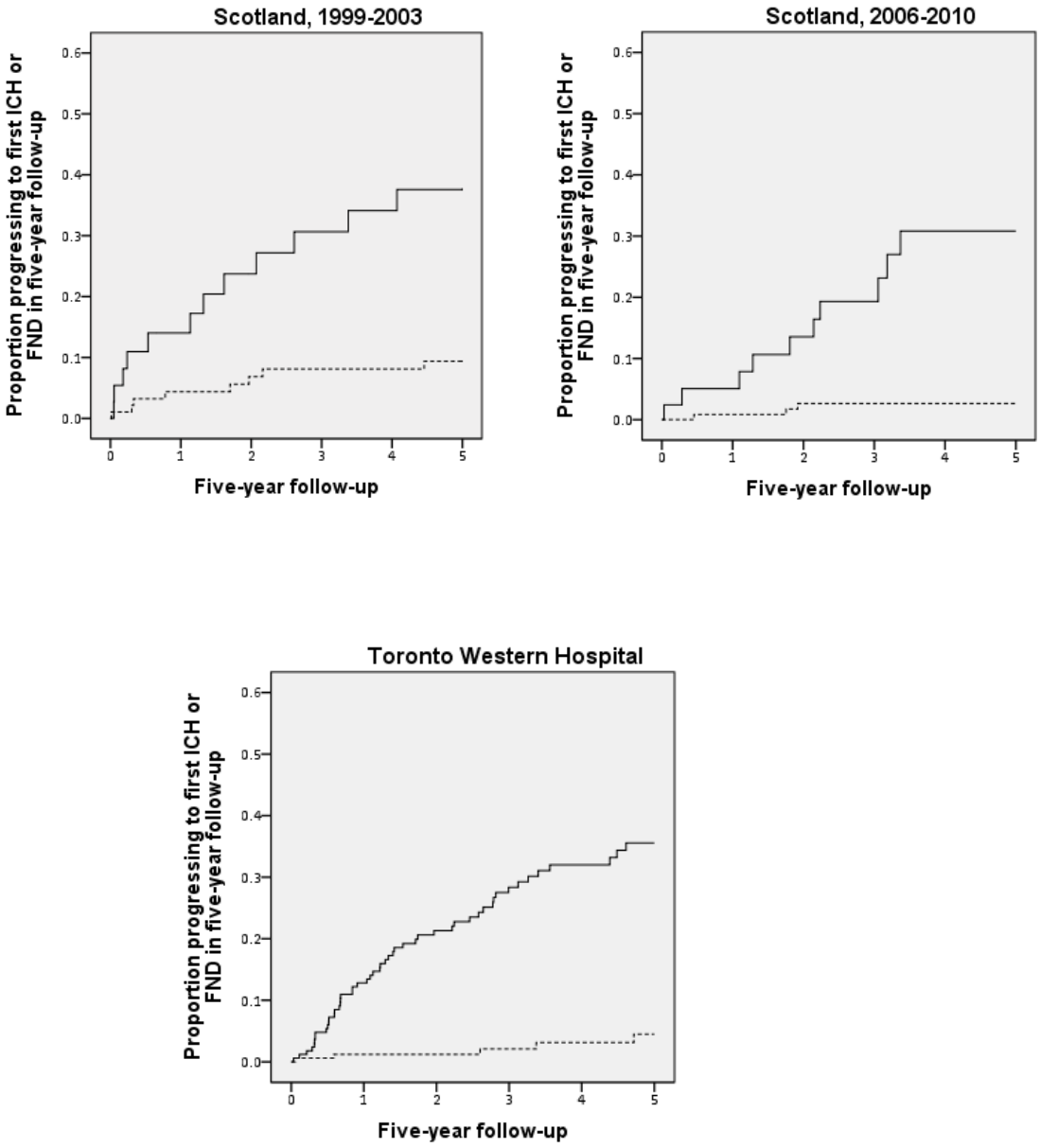



**Figure A. 2 Kaplan-Meier plots comparing estimated risk of first ICH or FND, stratified by presentation: ICH or FND presentation (continuous line) *vs* other presentation (dotted line)**

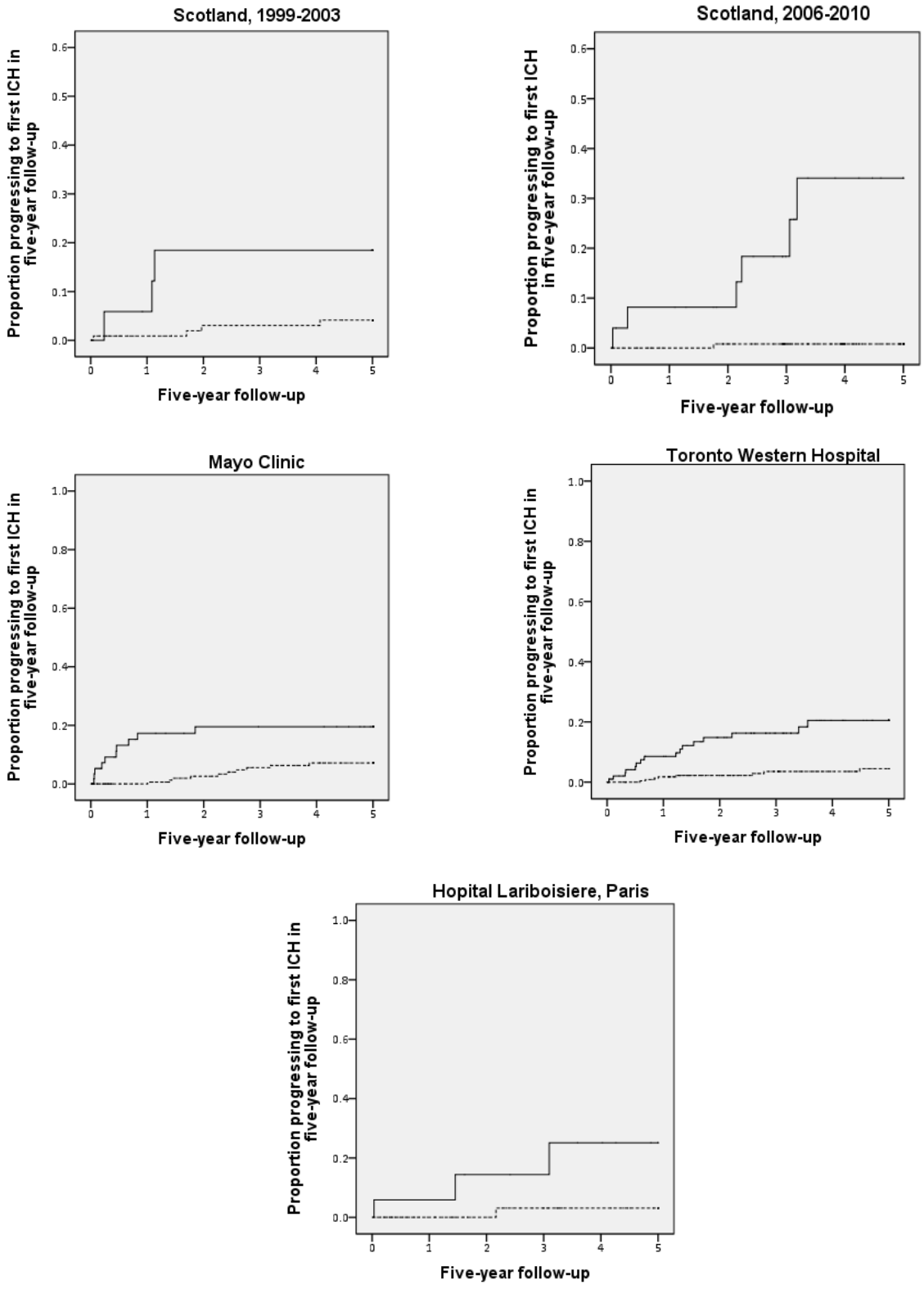



**Figure A. 3 Kaplan-Meier plots comparing estimated risk of first ICH, stratified by CCM location: brainstem (continuous line) *vs* other location (dotted line)**

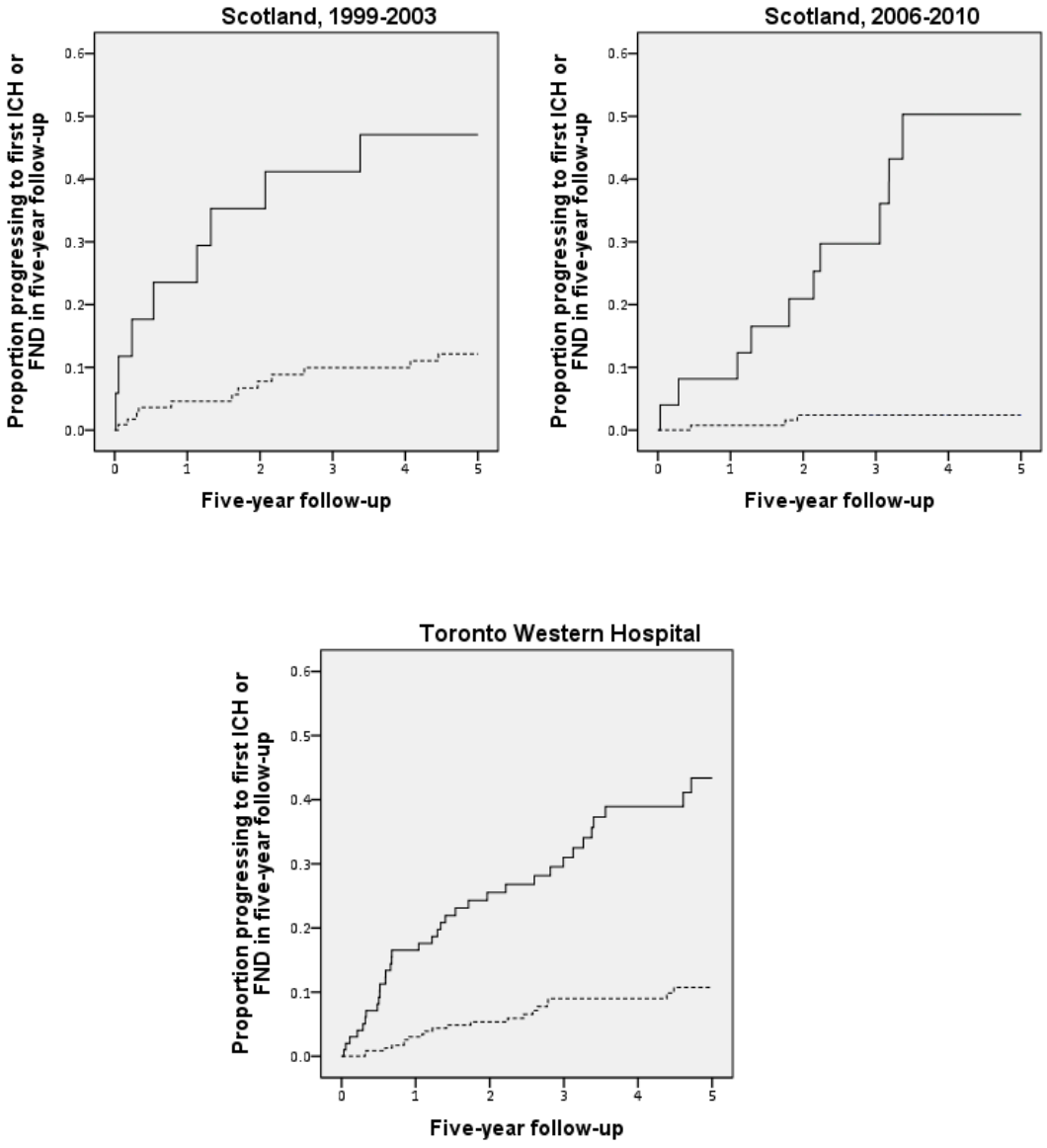



**Figure A. 4 Kaplan-Meier plots comparing estimated risk of first ICH or FND, stratified by CCM location: brainstem (continuous line) *vs* other location (dotted line)**

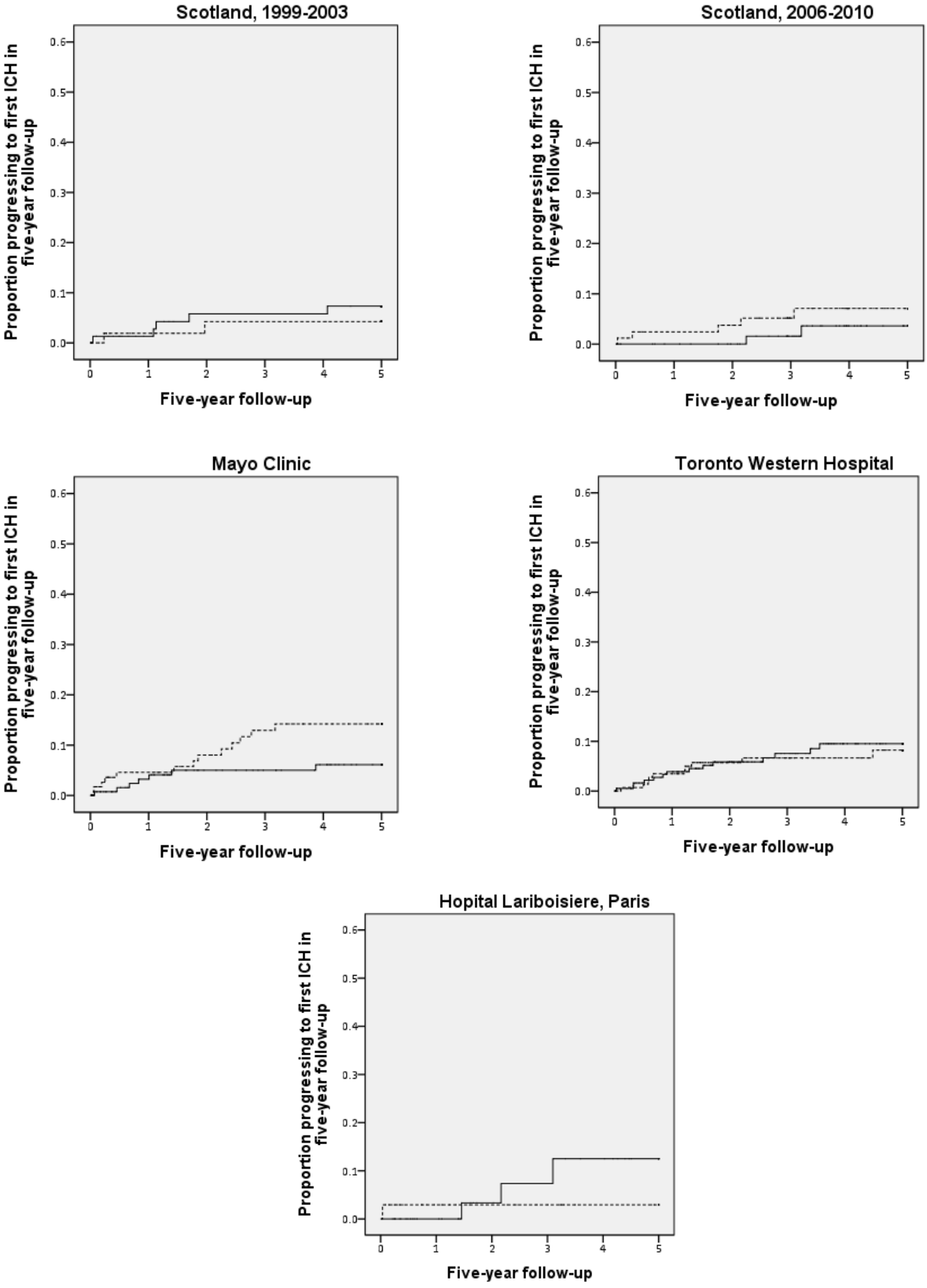



**Figure A. 5 Kaplan-Meier plots comparing estimated risk of first ICH, stratified by sex: female (continuous line) *vs* male (dotted line)**

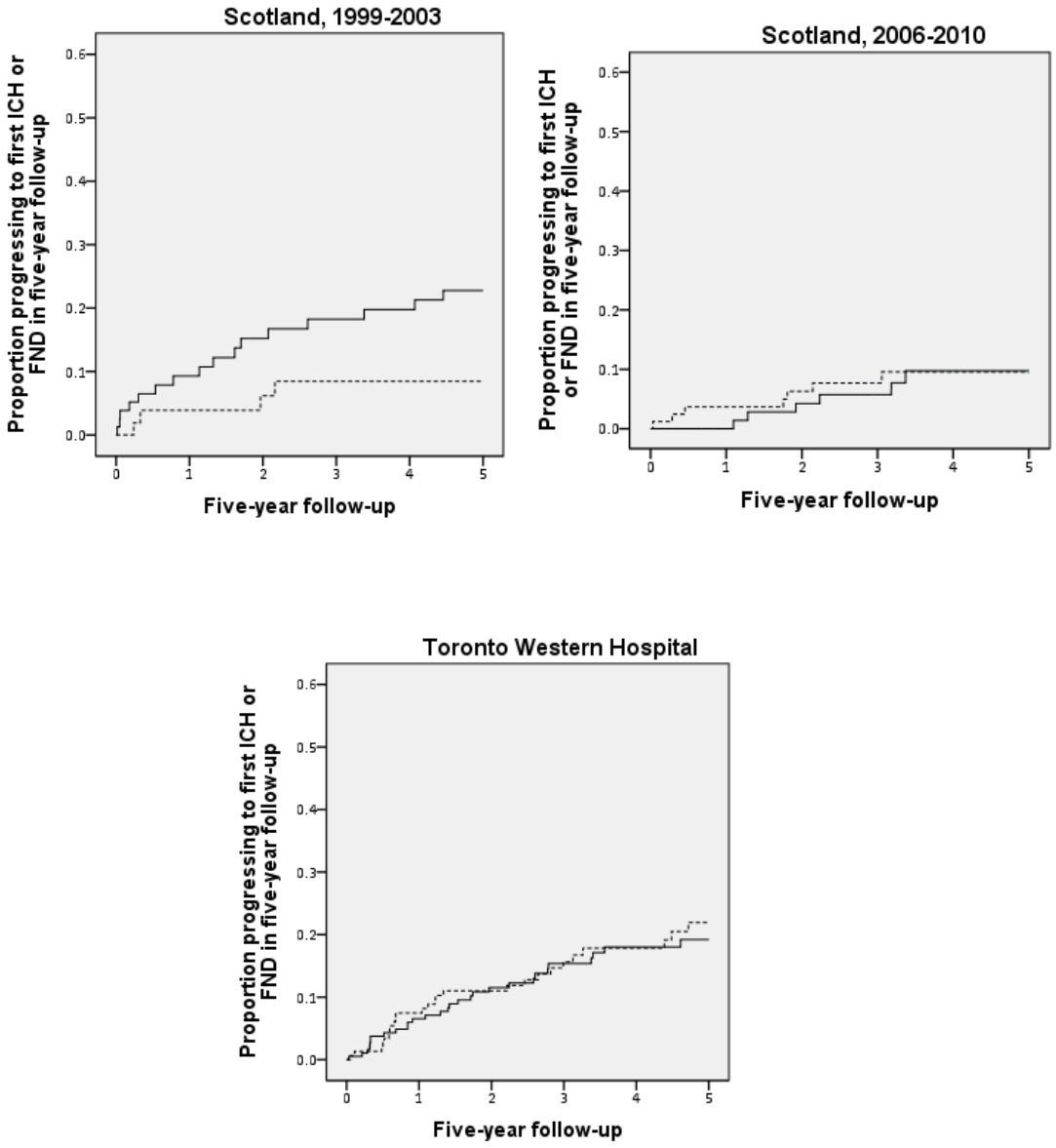
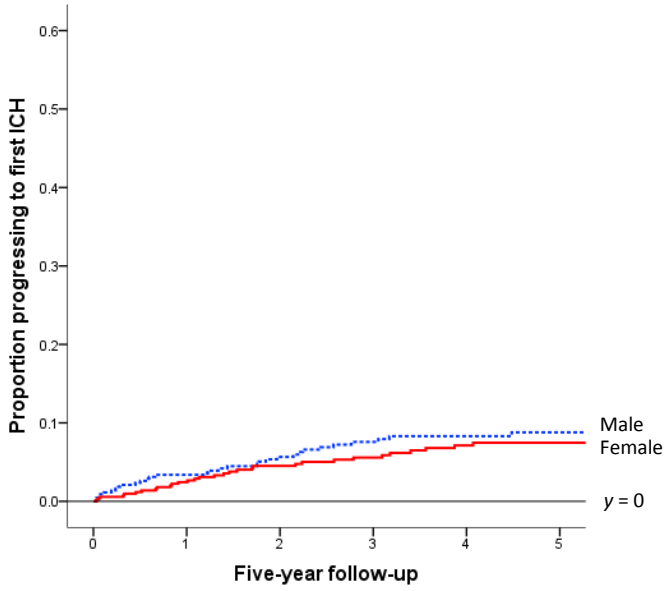



**Figure A. 6 Kaplan-Meier plots comparing estimated risk of first ICH or FND, stratified by sex: female (continuous line) *vs* male (dotted line)**

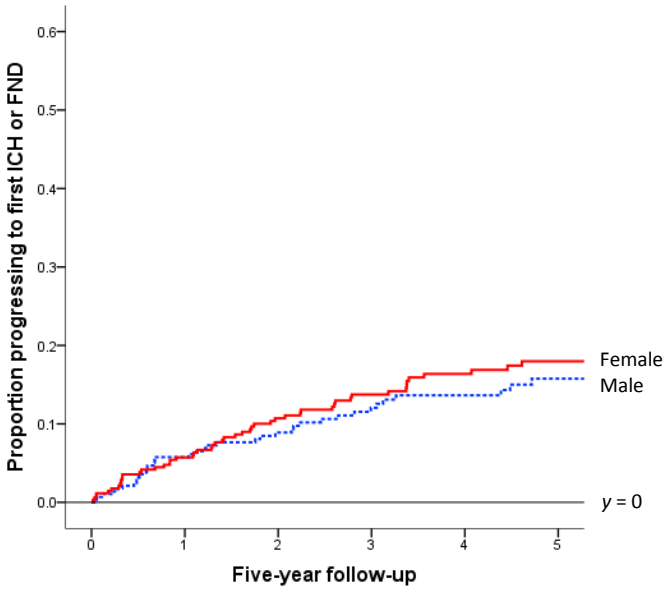
**(a)** **Five cohorts, pooled**




**Number of adults at risk (number of ICH in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Female:** | 541 | 454(12) | 381(9) | 328(4) | 271(5) | 230(1) |
| **Male:** | 447 | 366(14) | 312(8) | 257(6) | 206(2) | 167(1) |

**(b)** **Three cohorts, pooled**




**Number of adults at risk (number of ICH in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Female:** | 351 | 301(19) | 255(15) | 212(8) | 165(6) | 140(3) |
| **Male:** | 289 | 254(16) | 215(8) | 175(7) | 137(3) | 108(3) |

**Figure A. 7 Kaplan-Meier plot comparing estimated risk of (a) first ICH or (b) first clinical event, stratified by sex**

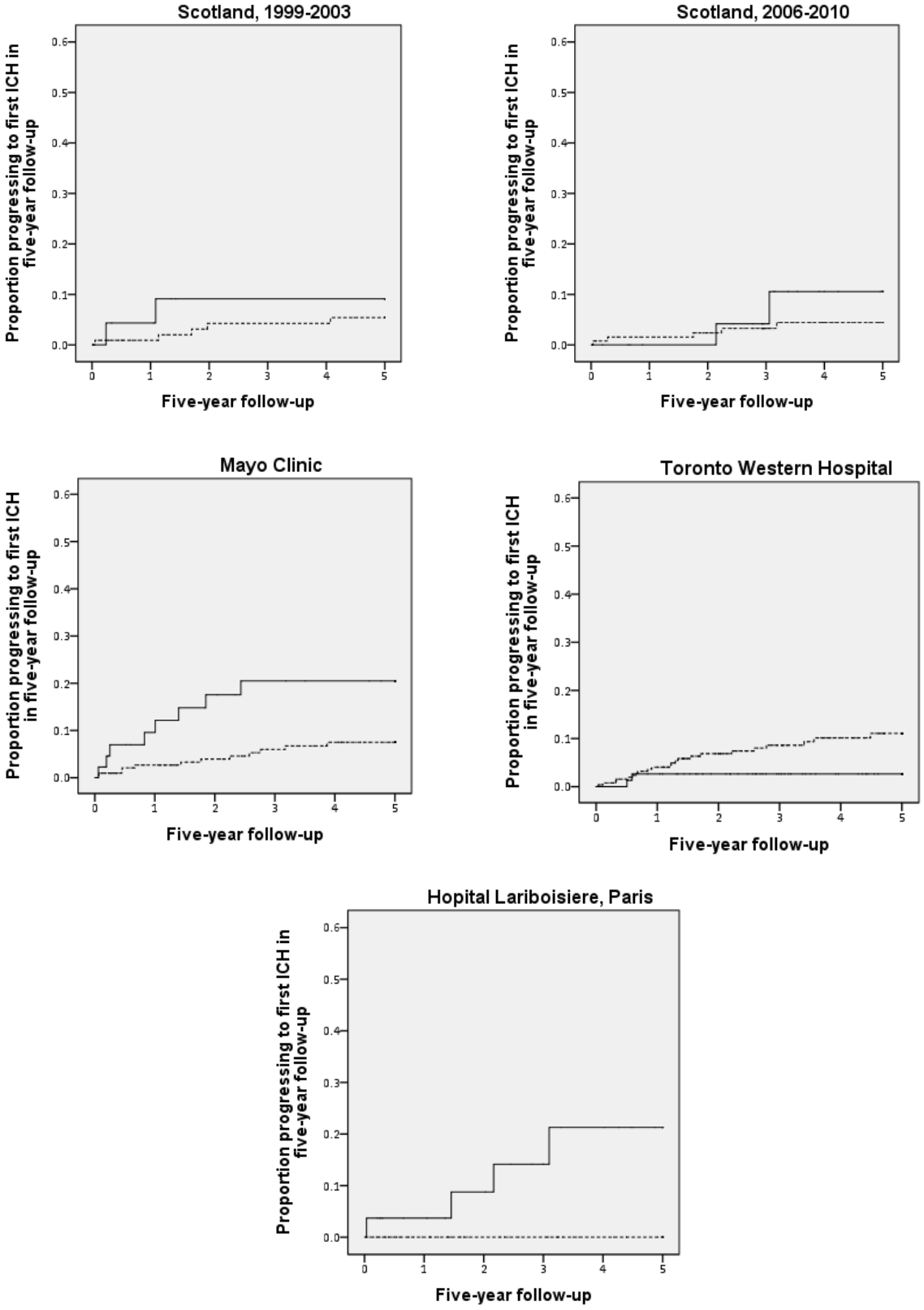



**Figure A. 8 Kaplan-Meier plots comparing risk of first ICH, stratified by CCM multiplicity: multiple CCM (continuous line) *vs* solitary CCM (dotted line)**

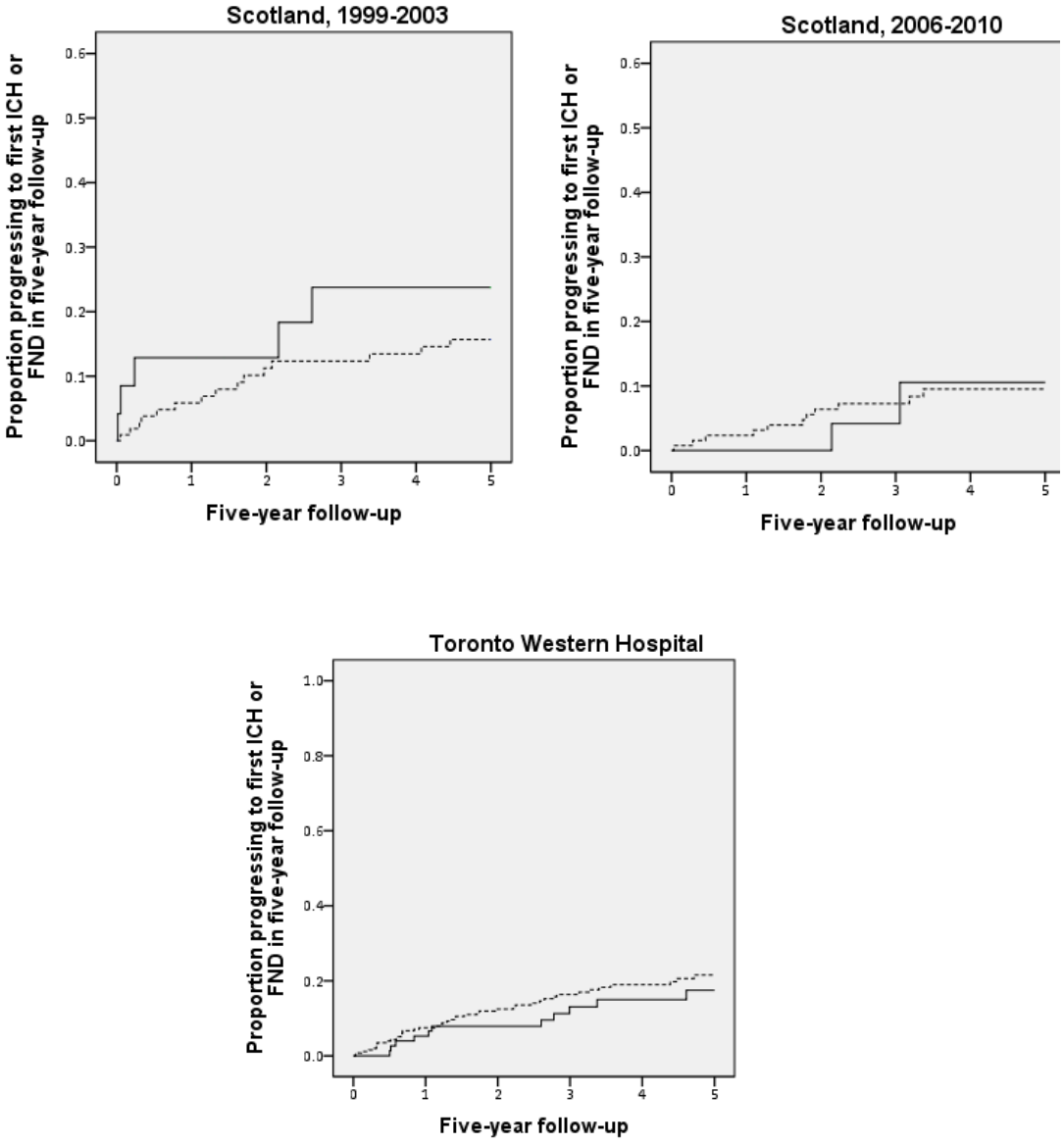
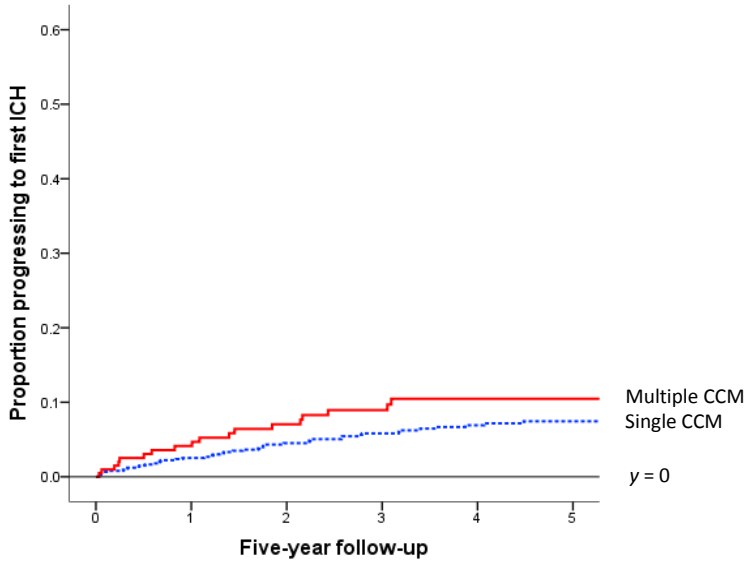



**Figure A. 9 Kaplan-Meier plots comparing estimated risk of first ICH or FND, stratified by CCM multiplicity: multiple CCM (continuous line) *vs* solitary CCM (dotted line)**

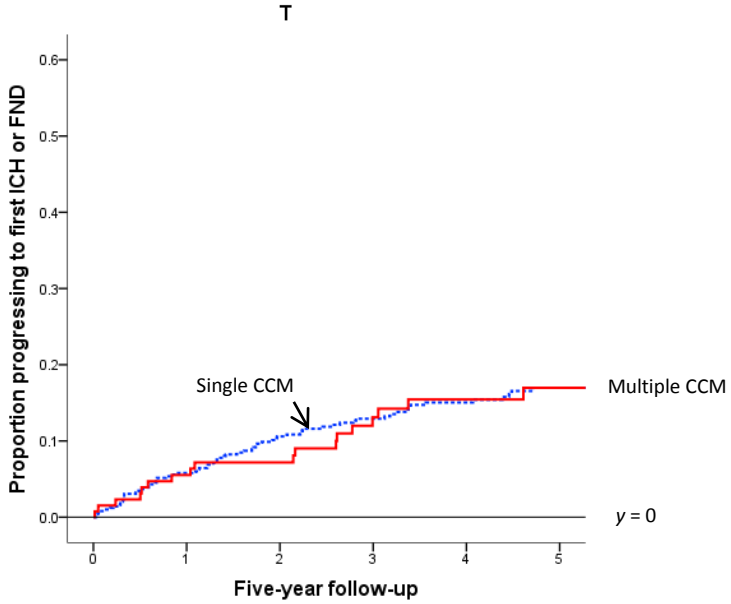
**(a)** **Five cohorts, pooled**




**Number of adults at risk (number of ICH in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Multiple** | 208 | 173(8) | 151(5) | 122(3) | 99(2) | 83(0) |
| **Single** | 780 | 647(18) | 542(12) | 463(7) | 378(5) | 314(2) |

**(b)** **Three cohorts, pooled**




**Number of adults at risk (number of ICH or FND in preceding year)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Multiple** | 132 | 115(7) | 102(2) | 79(6) | 61(2) | 52(1) |
| **Single** | 508 | 440(28) | 368(21) | 308(9) | 241(7) | 196(5) |

**Figure A. 10 Kaplan-Meier plots comparing estimated risk of (a) first ICH or (b) first clinical event, stratified by CCM multiplicity: multiple *vs* solitary CCM**

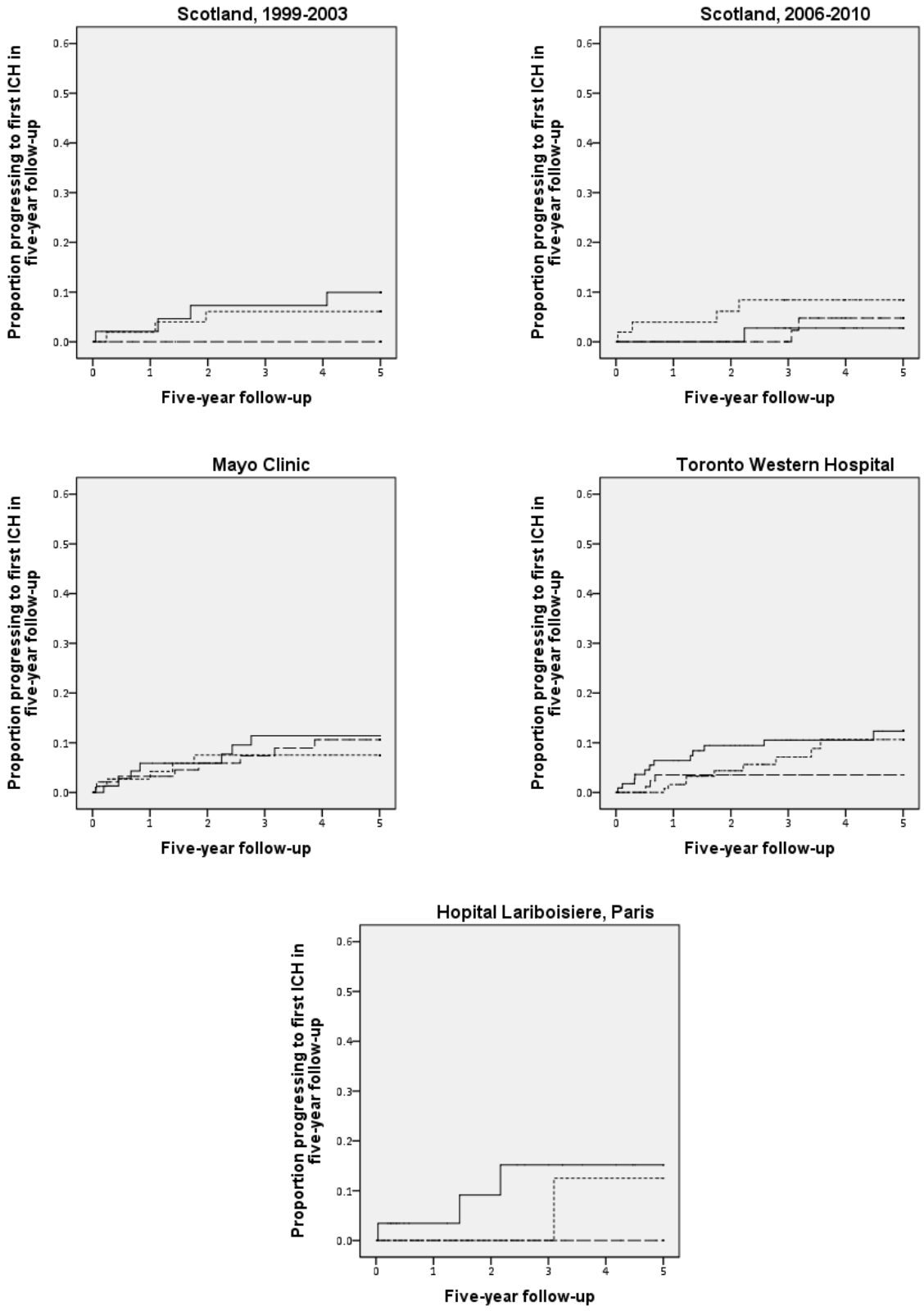



**Figure A. 11 Kaplan-Meier plots comparing estimated risk of first ICH, stratified by age-group: 35 years or younger (continuous line) *vs* 36-53 years (dotted line) *vs* 54 years or older (broken line)**

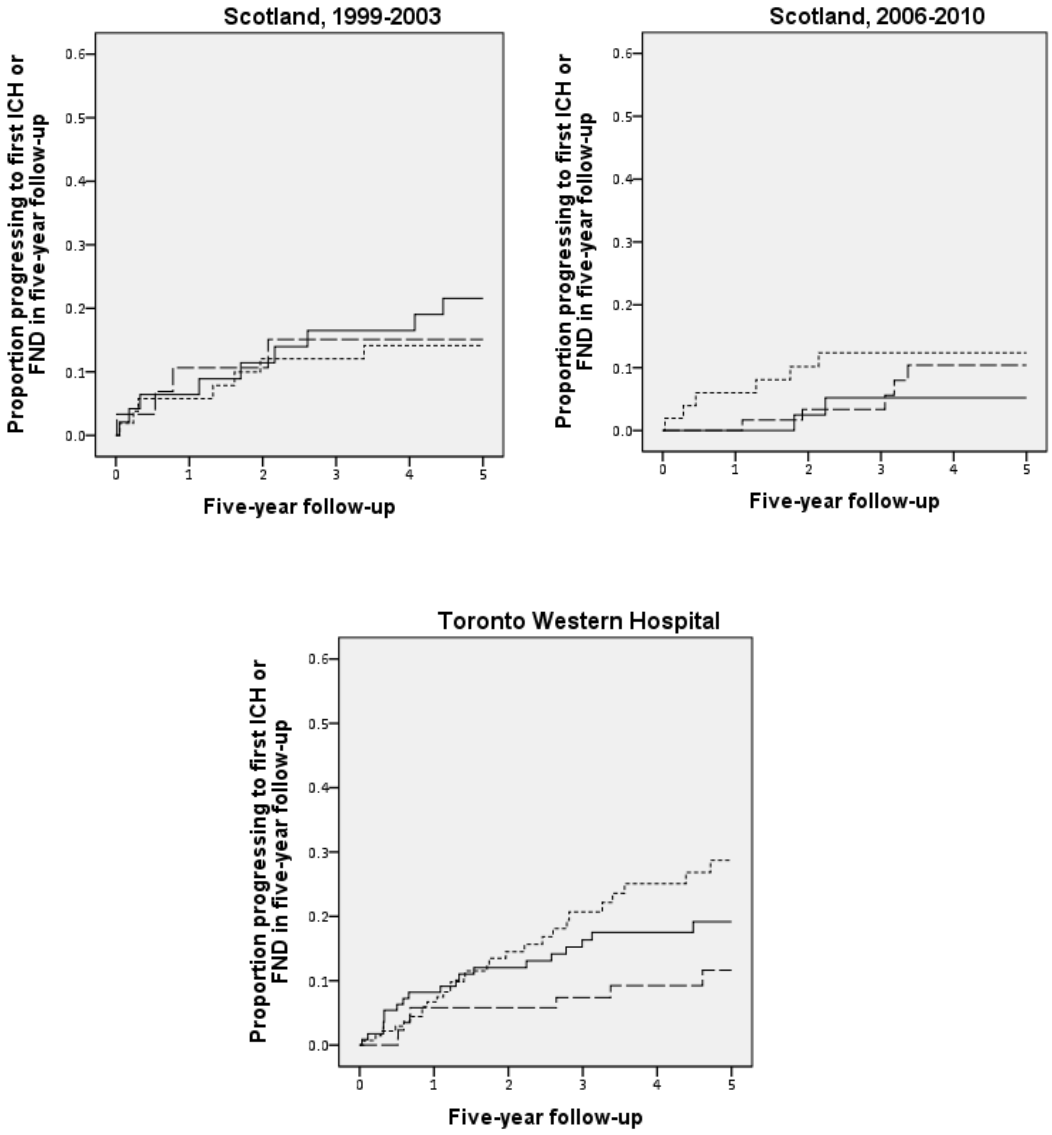
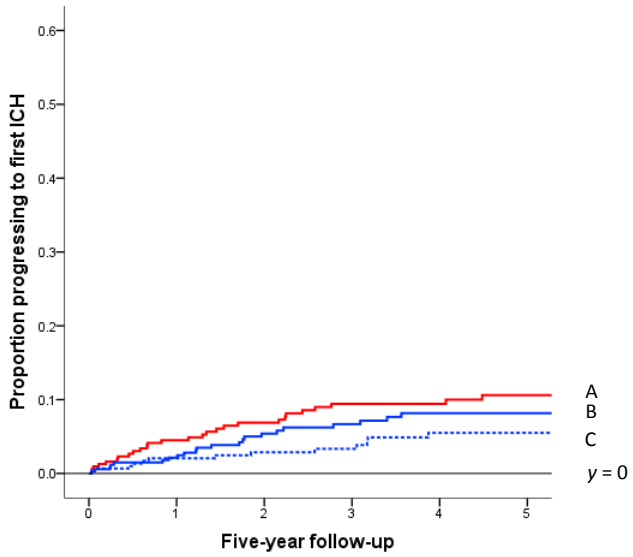


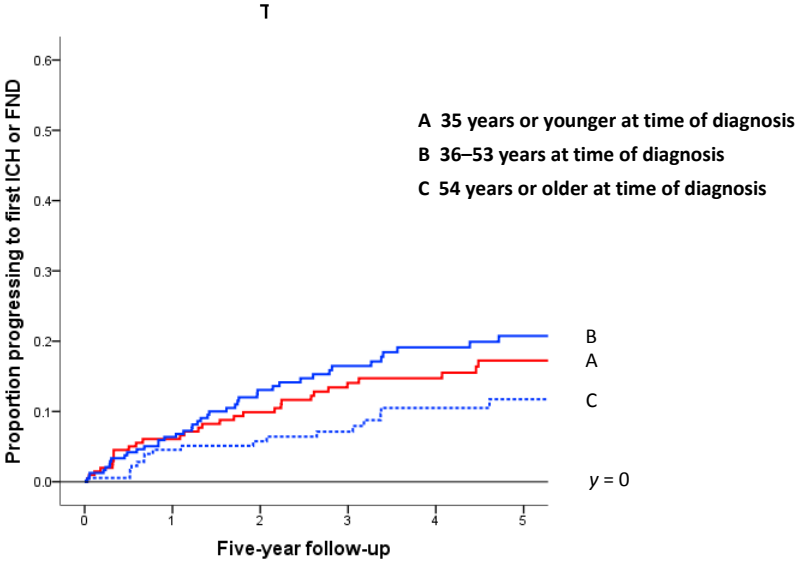

**Figure A. 12 Kaplan-Meier plots comparing estimated risk of first ICH, stratified by age-group: 35 years or younger (continuous line) *vs* 36-53 years (dotted line) *vs* 54 years or older (broken line)**

**(a)** **Five cohorts, pooled**



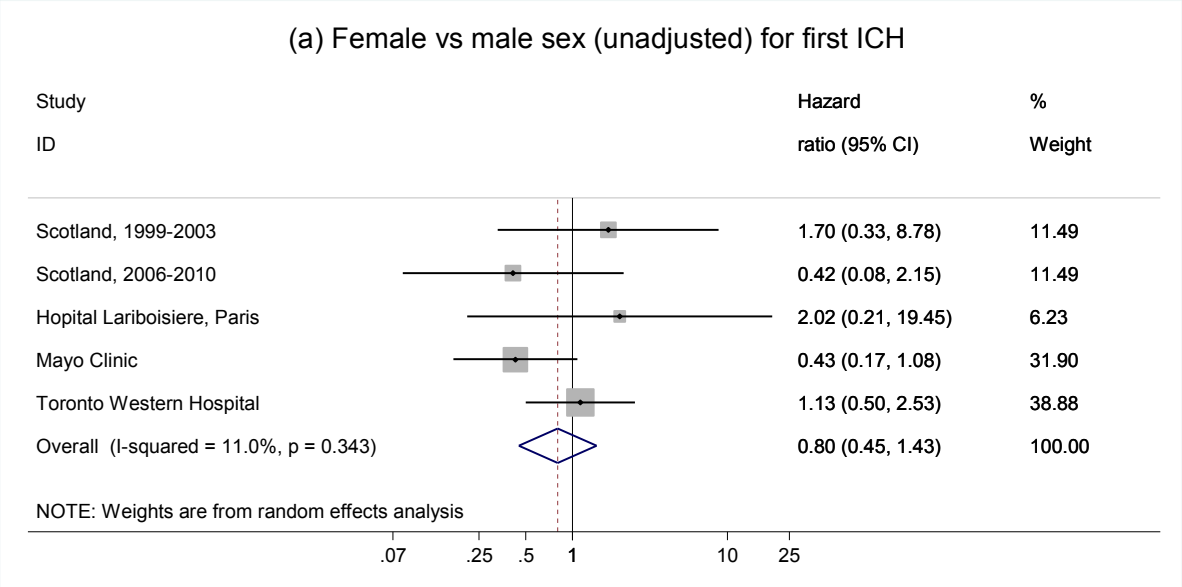

| Number of adults at risk (number of ICH in preceding year) | | | | | | |
|---|---|---|---|---|---|---|
| 35 years or younger at diagnosis | 322 | 254(13) | 226(6) | 196(6) | 161(0) | 134(2) |
| 36–53 years at diagnosis | 358 | 297(7) | 238(9) | 196(3) | 168(3) | 141(0) |
| 54 years or older at diagnosis | 308 | 269(6) | 229(2) | 193(1) | 148(4) | 122(0) |

**(b)** **Three cohorts, pooled**




| Number of adults at risk (number of ICH in preceding year) | | | | | | |
|---|---|---|---|---|---|---|
| 35 years or younger at diagnosis | 210 | 176(12) | 159(7) | 136(7) | 108(1) | 89(3) |
| 36–53 years at diagnosis | 247 | 214(15) | 166(14) | 132(6) | 109(4) | 91(2) |
| 54 years or older at diagnosis | 183 | 165(8) | 145(2) | 119(2) | 85(4) | 68(1) |

**Figure A. 13 Kaplan-Meier plots comparing estimated risk of (a) first ICH or (b) first clinical event, stratified by age-group**



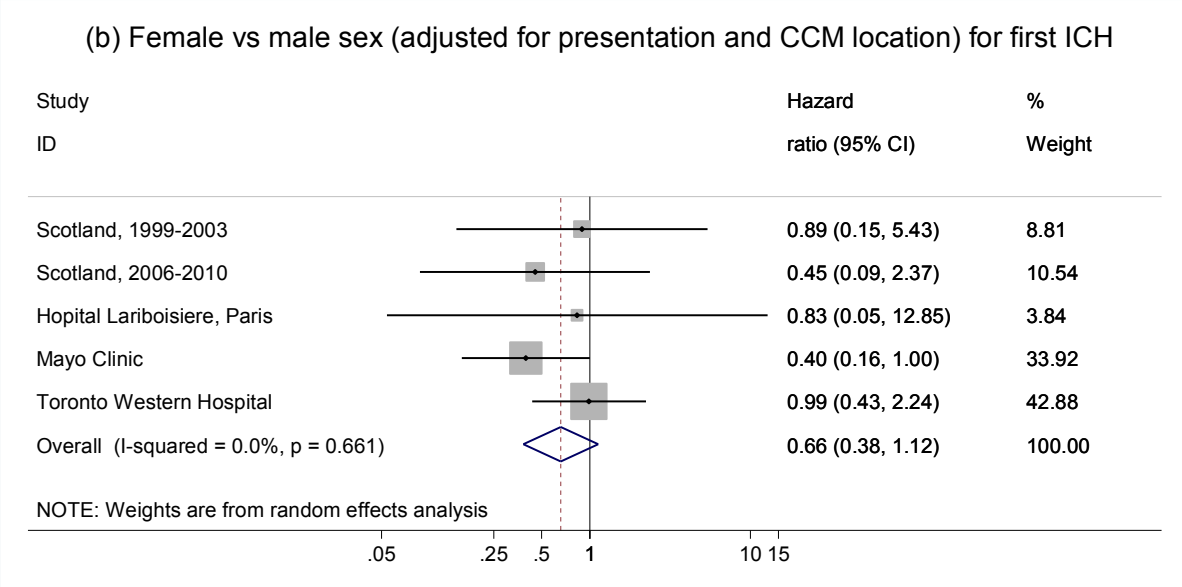




**Figure A. 14 Forest plots displaying random-effects meta-analyses for sex, (a) unadjusted and (b) adjusted for the two core predictors, for ICH only**

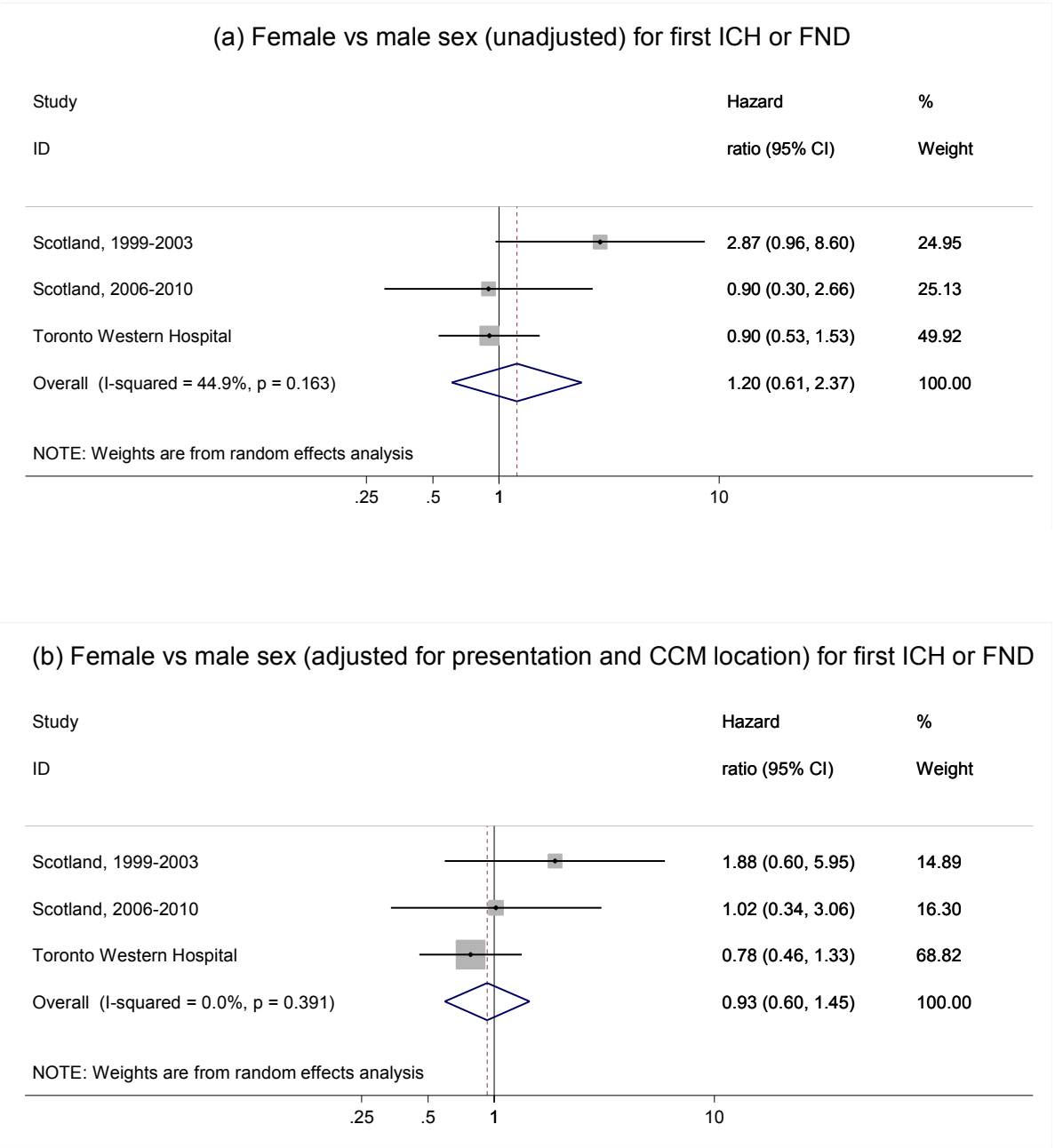
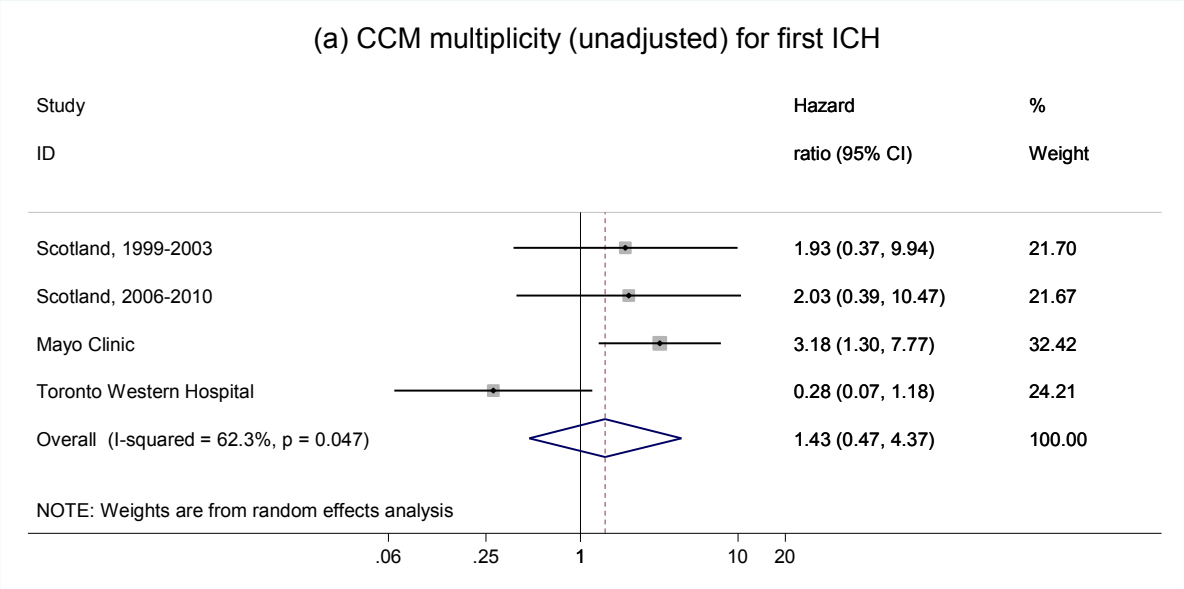
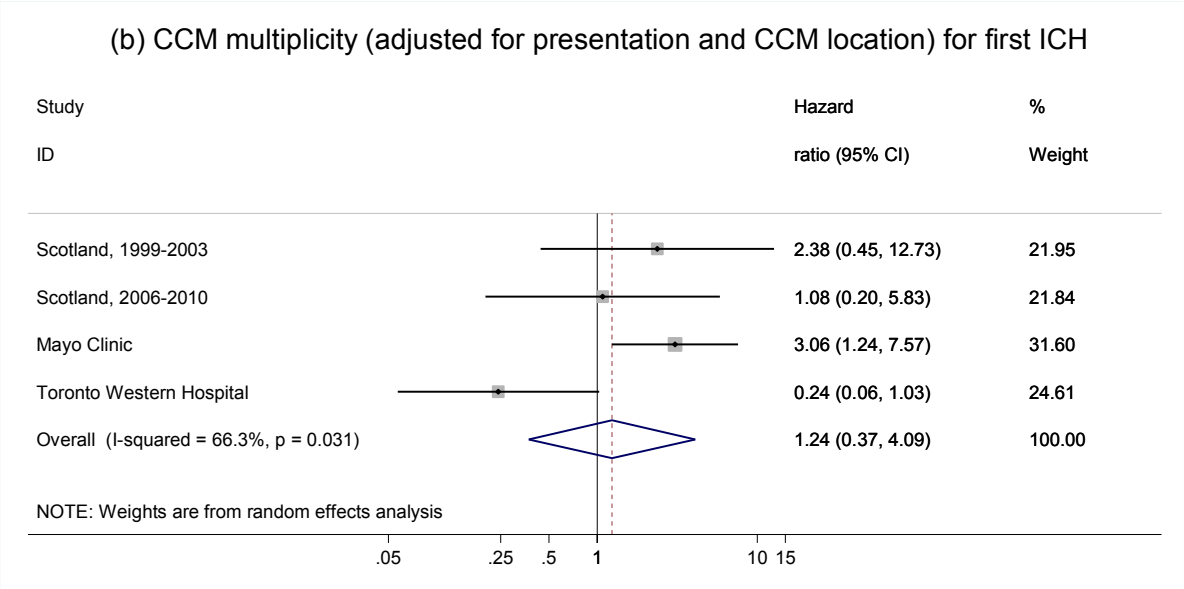



**Figure A. 15 Forest plots displaying random-effects meta-analyses for sex, (a) unadjusted and (b) adjusted for the two core predictors, for ICH or FND**




***Note*** The Parisian cohort was not included in these meta-analyses because only adults with multiple CCMs suffered an intracranial haemorrhage, and therefore hazard ratios could not be obtained for that cohort

**Figure A. 16 Forest plots displaying random-effects meta-analyses for CCM multiplicity, (a) unadjusted and (b) adjusted for two core predictors, for ICH only**

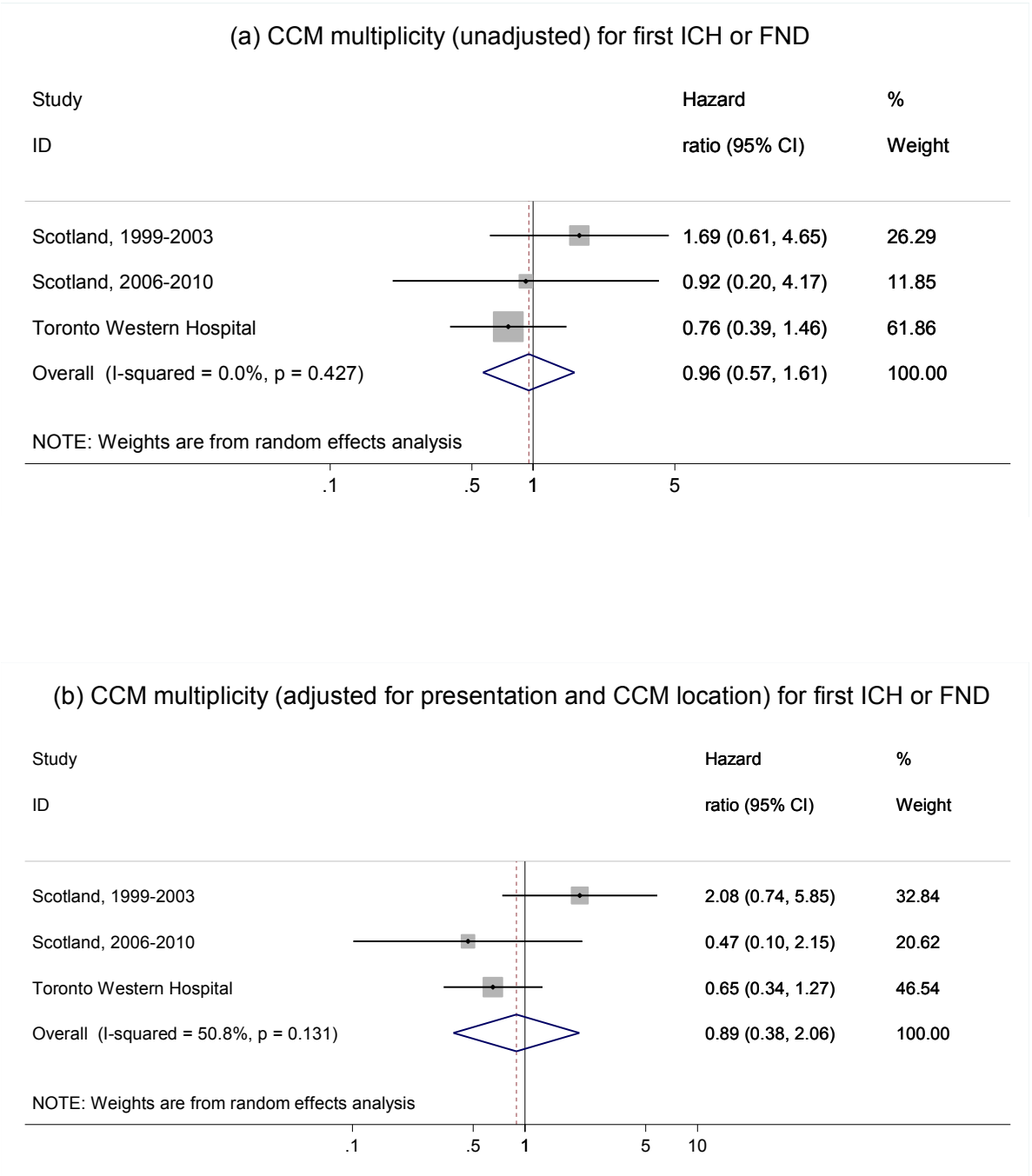
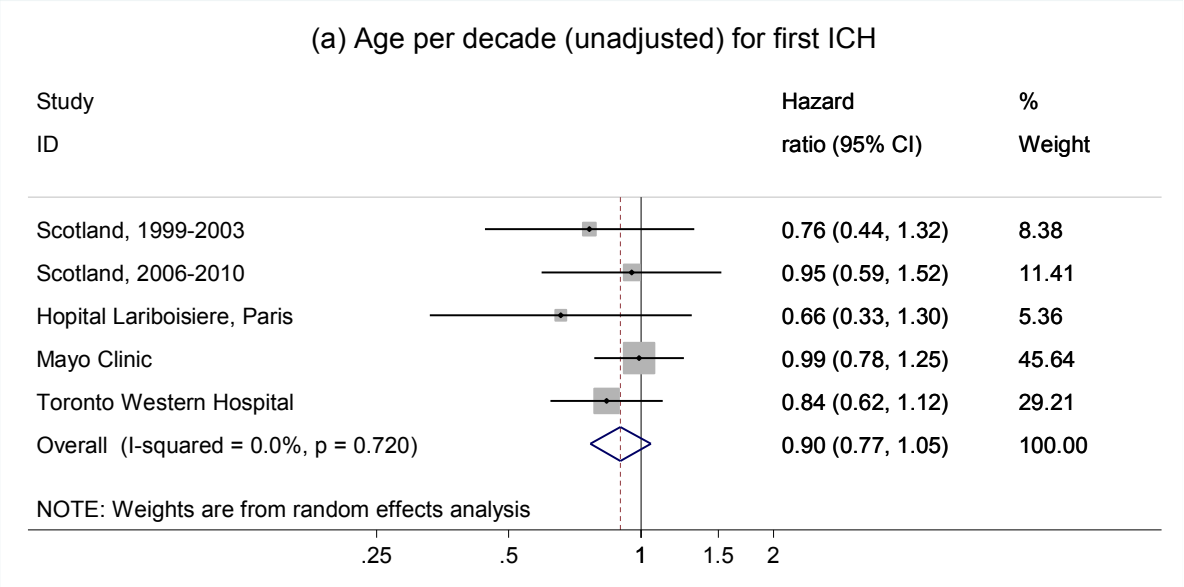



**Figure A. 17 Forest plots displaying random-effects meta-analyses for CCM multiplicity, (a) unadjusted and (b) adjusted for two core predictors, for ICH or FND**



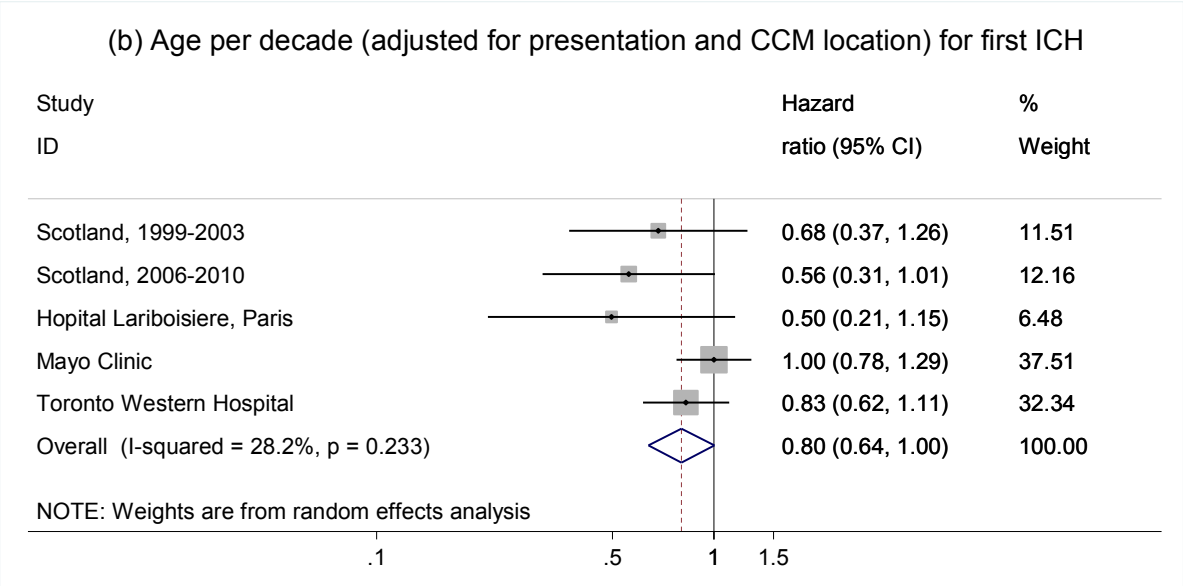




**Figure A. 18 Forest plots displaying random-effects meta-analyses for age, (a) unadjusted and (b) adjusted for two core predictors, for ICH only**

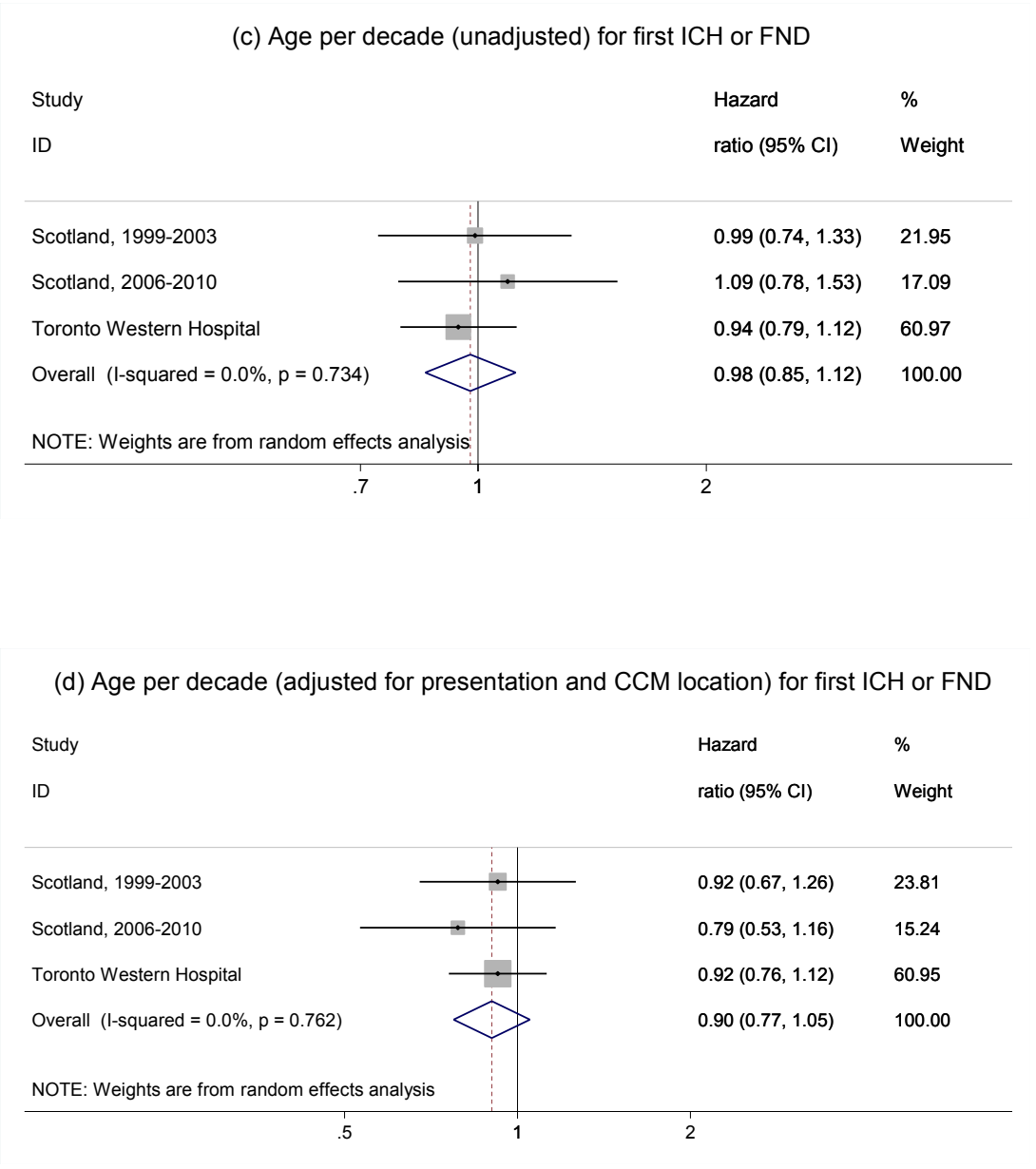



**Figure A. 19 Forest plots displaying random-effects meta-analyses for age, (a) unadjusted and (b) adjusted for two core predictors, for ICH or FND**